There was evidence that total staff, RN, and LPN hours had positive effects on some resident outcomes and magnitude of effect differed for different nursing staff.

Conclusions. No definitive conclusion could be drawn on whether changing nursing staff time or nursing staff coverage models would affect residents' outcomes based on the research evidence gathered in the SR. RWE analysis helped to fill a gap in the available published literature and allowed policy makers to better understand the impact of revising current regulations based on actual outcomes.

OP49 MAIC-ing Use Of Trials? Study Of Matching-Adjusted Indirect Comparisons

Joy Leahy (jleahy@stjames.ie) and Cathal Walsh

Introduction. When conducting a Network Meta-Analysis (NMA) for a Health Technology Assessment (HTA), the submitting company typically will have access to Individual Patient Data (IPD) from their own trials, but only aggregate data (AgD) for the comparator. In this case, they can re-weight the IPD so that the covariate characteristics in the IPD trials match that of the AgD trials, using the increasingly popular method of Matching-Adjusted Indirect Comparison (MAIC).

Methods. We carried out a simulation study to investigate this method in a Bayesian setting. We simulated three IPD trials comparing treatments A and B (AB-IPD trials), and one aggregate data trial comparing treatments B and C (BC-AgD trial). We investigated two options of weighting covariates: 1. all three studies are weighted separately to match the BC-AgD trial (MAIC Separate Trials). 2. patients are weighted across all three IPD studies to match the BC-AgD trial, but the NMA still considers each trial separately (MAIC Pooled Trials). We compared the results of the MAIC to a standard NMA and a mixed IPD/AgD NMA. We applied these methods to a network of treatments for multiple myeloma.

Results. MAIC can provide more accurate estimates of the relative treatment effects than a standard NMA in the BC-AgD trial population. However, MAIC may decrease the accuracy of the relative treatment effects in the overall population. Treatment rankings were unchanged when applying MAIC to the multiple myeloma network.

Conclusions. MAIC is beneficial as a sensitivity analysis to demonstrate that results hold across patient populations. If there is a difference in relative treatment effects attributable to population imbalances, then it is useful to be able to quantify this difference. However, we recommend using either a standard NMA or a mixed IPD/AgD NMA for the base case analysis, given the potential bias that can arise in an MAIC.

OP50 IQWiG And GRADE – An Exemplary Comparison Of Methods

Lisa Schell (lisa.schell@iqwig.de), Stefan Sauerland, Stefanie Thomas, Thomas Kaiser, Miriam Luhnen, Martina Lietz and Guido Skipka

Introduction. Efforts to harmonize health technology assessment (HTA) processes and methods across Europe are currently intensified. In this context, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach has been proposed as a "common ground" in joint HTAs. However, GRADE has been primarily developed to support authors of clinical guidelines. Therefore, it is unclear whether HTA reports based on GRADE are compatible with the methods currently applied by European HTA organizations.

Methods. We contrasted IQWiG's methods paper and publications by the GRADE Working Group with regard to the following domains: 1) risk of bias (RoB) assessment 2) prerequisites for "greater benefit" (assuming that IQWiG's "greater benefit" corresponds to a GRADE assessment of at least low certainty and a small important effect) and 3) consideration of non-randomized studies (NRS). We present illustrative differences and highlight similarities.

Results. Overall, RoB assessments are very similar under both approaches. However, we identified several important differences. In case of very severe publication bias, IQWiG methods preclude drawing a conclusion, whereas GRADE requires only downgrading the certainty of evidence while still allowing for a conclusion on effect sizes. Secondly, IQWiG generally requires a statistically significant effect for a "greater benefit", while GRADE does not (statistically non-significant effects would only necessitate downgrading the certainty of results for imprecision). Another difference is that in general, NRS are not included in IQWiG assessments when randomized studies (RS) are available and thus possible. In contrast, preliminary GRADE guidance recommends considering NRS in addition to RS when the RS evidence is of low or very low certainty.

Conclusions. While GRADE and IQWiG's method share some similarities, our exemplary analysis shows that there are some notable differences. Therefore, GRADE should not be used "out of the box" for European HTAs. To foster further discussion, more research (including a comprehensive comparison of methods and an analysis of resources for adaptation) is needed.

OP52 Use Of Intention To Treat And Magnitude Of Treatment Effects

Susan Armijo-Olivo (susanarmijo@gmail.com), Bruno Da costa, Chiara Arienti and Negrini Stefano

Introduction. Intention to treat (ITT) is a gold standard strategy to analyze the results of randomized controlled trials (RCTs). ITT analysis has been considered a methodological indicator of the quality of clinical trials. The extent to which the use of ITT is related to the treatment effects observed in RCTs has not been rigorously explored. Therefore, the main objective of this study was to determine the association between biases related to attrition and missing data and the use of intention to treat principle, and changes in effect size estimates in RCTs.

Methods. This was a meta-epidemiological study. A random sample of RCTs included in meta-analyses was identified. Data extraction including assessments of the use of intention to treat principle, missing data and drop-outs was conducted independently by two

https://doi.org/10.1017/S0266462319001168 Published online by Cambridge University Press

reviewers. To determine the association between biases related to attrition, missing data, and the use of intention to treat and effect sizes, a two-level analysis was conducted using a meta-meta-analytic approach.

Results. Three-hundred and ninety-three trials included in 43 meta-analyses, analyzing 44,622 patients contributed to this study. From these, 134 trials (34.1%) used ITT and 218 (55.5%) did not use ITT. Trials which did not use the ITT principle, or which were assessed as having an inappropriate control of incomplete outcome data (based on the Cochrane risk of bias tool) tended to underestimate the treatment effect when compared with trials with adequate use of ITT (ES= -0.13; 95%CI -0.26, -0.01) or trials which were assessed as having an appropriate control of incomplete outcome (ES= -0.18; 95%CI -0.29, -0.08).

Conclusions. Our results suggest that when evaluating risk of bias of primary RCTs, systematic reviewers should pay attention to these biases since they could underestimate treatment effects. Systematic reviewers should perform sensitivity analysis including trials with low risk of bias in these domains.

OP53 Health Technology Assessment Acceptability Of Innovative Survival Metrics In Oncology

Richard Macaulay (richard.macaulay@parexel.com)

Introduction. Most new oncology therapies are studied in the advanced/metastatic setting. However, there is an increasing focus on earlier stage disease. Nevertheless, measuring Overall Survival (OS) in neo-/adjuvant therapy trials can be very challenging due to the increased life expectancy and the confounding effects of subsequent treatments. Thus, their primary endpoints tend to be surrogate survival metrics (e.g. metastases-free survival). This research aims evaluates the health technology assessment (HTA) acceptability of such endpoints through recent neo-/adjuvant HTA assessments.

Methods. The European Medicines Agency (EMA) website was screened for any neo-/adjuvant oncology therapies approved (1 January 2013-22 October 2018) and any corresponding publicly-available assessments by HTA bodies (NICE, SMC, IQWiG, G-BA, CADTH, PBAC, HAS) were identified and key data extracted.

Results. Six neo-/adjuvant therapies have received marketing authorization by the European Commission (EC). These six have been on the market for an average of 8.9 months (range: 0.9-39.3 months, median: 3.3 months). In four of the six, the pivotal trial primary endpoints were measures of relapse-/disease-free survival, (others: pathological complete response and PFS/OS co-primary). Only one had mature OS data available at EC-approval. Four of the six therapies had received at least draft guidance by an HTA body, encompassing 11 HTA assessments in total (4: NICE, 2: IQWiG, HAS; 1: SMC, CADTH, G-BA). Only two of 11 (18%) were positive outcomes (both NICE), the remaining nine were negative.

Conclusions. Oncology therapies are increasingly receiving regulatory approval in the neo-/adjuvant setting. However, their pivotal trials are frequently powered to show benefits in disease-/metastases-free survival. Whilst sufficient for regulatory approval, translating this to favorable HTA decisions has been more challenging. Clearly establishing linkages between surrogate survival metrics and OS alongside measuring metrics that clearly portray patient benefits (e.g. time to symptomatic progression) could improve HTA-acceptability. Further, some payers allow for temporary reimbursement whilst additional evidence is generated (e.g. Cancer Drugs Fund in England).

OP54 Monitoring Evidence On Overall Survival Benefits Of Anti-Cancer Drugs

Nicole Grössmann (Nicole.Groessmann@hta.lbg.ac.at), Martin Robausch, Katharina Rosian, Claudia Wild and Judit Simon

Introduction. The introduction of fast-track licensing strategies increases the approval of anti-cancer drugs with ambiguous benefit-risk profiles. Thus, in many instances there is lacking evidence about overall survival (OS) at the time of marketing authorisation. Our objective was to monitor and characterise therapies with ambiguous benefit-risk profiles and identify any post-approval updates on median OS after at least three years of approval by the European Medicines Agency (EMA).

Methods. We included all originator anti-cancer drugs with initially ambiguous benefit-risk profiles that received marketing authorization from the EMA between 1 Jan 2009 and 31 May 2015. Our monitoring timeframe was at least three years after EMA-approval. To identify study updates, the following three sources were included: clinicaltrials.gov, European Public Assessment Reports (EPARs), and PubMed.

Results. In total, we identified 102 eligible approval studies. Out of these, a negative difference in median OS or no information was available in forty-three (42.2%) instances. During monitoring, eleven updates with accessible information on median OS could be identified. Including monitoring results, there are still thirty-two remaining therapies (31.4%) where no or negative information (n = 27 [26.5%] and n = 5 [4.9%], respectively) regarding median OS was present at least three years after EMA approval.

Conclusions. One-third of oncology drugs with ambiguous benefit-risk profiles failed to demonstrate a survival benefit even several years following marketing authorization. Systematic and transparent post-approval monitoring mechanisms will be of high relevance to assure a clinically relevant patient benefit, since the trend towards faster access to medicines with uncertain benefit is increasing rather than declining.

OP56 Are Therapeutic Positioning Reports Driving Pharmaceutical Reimbursement Outcomes In Spain?

Raquel Fernandez Dacosta (Raquel.FernandezDacosta@PAREXEL.com), Andrea Berardi and Richard Macaulay

https://doi.org/10.1017/S0266462319001168 Published online by Cambridge University Press