year during the observation (post-index) period. Costs were compared between cohorts using cost ratios (CR), and confidence intervals (CI) and p-values were generated using non-parametric bootstrap procedures. ***Results:*** In total 92 and 218 patients were included in the pembrolizumab and nivolumab cohorts, respectively. After weighting, mean age was 55 years in both cohorts, while the proportion of females was lower in the pembrolizumab (35.3%) compared to the nivolumab cohort (44.1%). Mean Quan-Charlson comorbidity index score was well balanced (pembrolizumab: 4.2; nivolumab: 4.3). During the observation period (pembrolizumab: 295 days; nivolumab: 274 days), pembrolizumab initiators had significantly lower all-cause hospitalization costs (CR [95% CI]: 0.29 [0.06-0.76], p=0.016) and cHL-related hospitalization costs (CR [95% CI]: 0.09 [0.00-0.31], p<0.001) than nivolumab initiators. All-cause and cHL-related outpatient visit costs were not statistically different between cohorts. ***Conclusions:*** In this real-world study, adult cHL patients initiated on pembrolizumab had significantly lower all-cause and cHL-related hospitalization costs compared to patients initiated on nivolumab.

Economic Evaluation Applications: Burden and Value of Therapies

ED1
ANTIMICROBIAL RESISTANCE IN US HOSPITALS: BURDEN AND VALUE OF INVESTMENT IN DEVELOPING NEW TREATMENTS

Iacobucci W,[1] Siego CV,[1] Dall T,[1] Wallin Bernhardsson N,[2] Ulrich J,[3] Dougherty JS[3]
[1]*IHS Markit, Washington, DC, USA,* [2]*IHS Markit, London, UK,* [3]*PhRMA, Washington, DC, USA*

Objectives: This research aims to quantify the burden of antimicrobial resistance (AMR) from the perspective of hospital stakeholders and the value of continued investment in developing new treatments. ***Methods:*** A dataset representative of the US population demographics and health characteristics was constructed by merging the American Community Survey, Behavioral Risk Factor Surveillance System and data on nursing home residents. Prediction equations linking patient demographics and health characteristics to likelihood of hospitalization within hospital service lines were generated using the Medical Expenditure Panel Survey and applied to the population file. Data from the National Healthcare Safety Network were used to calculate state-specific rates of AMR in hospitalized patients experiencing an infection. Peer-reviewed published research provided estimates for AMR-attributable outcomes, including mortality, inpatient days, and direct & indirect costs. Results were calculated under a base case scenario reflecting current rates of infection continuing into the future, and alternative scenarios reflecting changes in future rates of infection and resistance. ***Results:*** Base case results suggested approximately 4,100 AMR-attributable deaths would occur in the base modeling year, resulting in over $700 million in direct costs, increasing to 5,300 deaths and $907 million in direct costs by 2035. Under a scenario in which rates of resistance increase to 100%, reflecting a hypothetical scenario where alternative antimicrobial treatments are no longer effective, projected 2035 AMR-attributable deaths increase to 30,700 (480% increase from base case) and direct costs of $8.4 billion (826% increase from base case). Infections are projected be highest in general surgery and thoracic surgery service lines, where high infection risk could potentially make surgeries too risky to perform. ***Conclusions:*** Though its current burden is substantial, AMR's potential future burden is significantly more concerning. Investing in AMR prevention strategies will be necessary to reverse course with respect to increasing resistance.

ED2
ELEMENTS OF VALUE FOR GENE THERAPY: A SYSTEMATIC REVIEW

Kim E,[1] Raimundo K,[2] Marcum ZA,[1] Veenstra DL[1]
[1]*University of Washington, Seattle, WA, USA,* [2]*Genentech, South San Francisco, CA, USA*

Objectives: ISPOR recommends that value assessments include elements beyond traditional quality-adjusted life years (QALYs) and costs. We aimed to identify non-traditional value elements relevant to gene therapies as it is unclear to what extent they have been included in gene therapy value assessments. ***Methods:*** We searched PubMed and Embase for full-text articles discussing non-traditional value elements defined by the 2018 ISPOR framework in the context of gene therapy that were published in English between 2015-2020. Health technology assessment (HTA) reports published by the Institute of Clinical and Economic Review and National Institute for Health and Care Excellence were collected. Articles and reports were included if they proposed methods for incorporation or accounted for specified value elements in economic evaluations or real-world decision making. ***Results:*** Twenty-four of 644 articles identified met inclusion criteria; 17 were peer-reviewed journal articles and 8 HTA reports. Disease areas for which specific gene therapies were discussed included cancer, beta thalassemia, inherited eye disease, hemophilia, spinal muscular atrophy, and severe immunodeficiency. The most common non-traditional value elements were productivity (n=12), severity of disease (n=10), equity (n=4), and scientific spillover (n=4). Productivity was captured as an indirect cost in cost-effectiveness analyses (CEAs). Although severity of disease, equity, and scientific spillover were not explicitly quantified, they were incorporated into HTA body decisions: severity through conditional market access, QALY weighting, higher CEA thresholds, and lower discount rates; equity through higher CEA thresholds and QALY weighting; and scientific spillover through accelerated market access. Multi-criteria decision analysis was also proposed. ***Conclusions:*** Use of novel value elements for gene therapies appears to be sparse in health economic studies to date. Methods of QALY weighting, varying CEA thresholds, discount rates, and specialized access pathways accounted for novel elements in value assessments. Future research on the feasibility, quantification, and incorporation of novel value elements for gene therapies is warranted.

ED3
SOCIETAL BURDEN OF DEMENTIA-RELATED PSYCHOSIS IN THE US: A COST OF ILLNESS ANALYSIS

Rajagopalan K,[1] **Rashid N,**[2] Abler V,[2] Shah A[3]
[1]*An-L-It-Iks Inc, Framingham, MA, USA,* [2]*ACADIA Pharmaceuticals Inc., San Diego, CA, USA,* [3]*An-L-It-Iks Inc, Somerville, MA, USA*

Background: Dementia-related psychosis (DRP), characterized by hallucinations and delusions, may accelerate the cognitive/functional decline among patients with dementia. Such declines have debilitating consequences on patients, caregivers, and society. While previous research has estimated total annual-direct DRP costs, analysis of both direct and indirect costs is important in understanding the overall societal burden of DRP. ***Objectives:*** To estimate the societal burden and associated costs of DRP in the US population. ***Methods:*** A Markov model was developed to assess the societal cost burden of DRP. The five DRP health states in the model were: mild, moderate, severe, end-of-life-care, and death as an absorbent health state. Cycle length was 30-days. Societal costs were calculated as a sum of total annual direct and indirect costs. Total indirect costs included both formal (paid by Medicare, Medicaid, or LTC insurance) and informal (caregiver time and patient out-of-pocket costs) caregiver costs, respectively. Prevalence, disease-severity, transition probabilities, and costs were derived from the literature. One-way sensitivity analysis was conducted to test the model's robustness by varying inputs and assumptions. ***Results:*** The estimated total annual-societal cost of DRP is $263B, and approximately $122B (46%) and $141B (54%) were indirect and direct costs, respectively. Of the total indirect costs, formal and informal caregiver costs including end-of-life-care costs were approximately $44.75B and $77.25B, respectively. End-of-life-care contributed $10B and $22B of the total formal and informal caregiver costs, respectively. ***Conclusions:*** Results of this analysis demonstrate that indirect costs contribute to approximately half of the total annual societal DRP costs; with caregiver costs contributing nearly 30% of the total. Given the aging US population, in addition to direct costs, indirect costs related to the caregiver and out-of-pocket costs may impose an enormous burden on the healthcare system. Given this public health concern, better management strategies and improved therapeutic options for DRP are needed.

ED4
ECONOMIC BURDEN OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) AMONG CHILDREN AND ADOLESCENTS IN THE UNITED STATES (US): A SOCIETAL PERSPECTIVE

Adler LA,[1] Childress A,[2] Cloutier M,[3] Gagnon-Sanschagrin P,[3] Davidson M,[3] Kinkead F,[3] Guerin A,[3] Lefebvre P,[4] **Schein J**[5]
[1]*NYU Grossman School of Medicine, New York, NY, USA,* [2]*Center for Psychiatry and Behavioral Medicine, Las Vegas, NV, USA,* [3]*Analysis Group, Inc., Montreal, QC, Canada,* [4]*Analysis Group, Inc., Montréal, QC, Canada,* [5]*Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, USA*

Objectives: To comprehensively assess the economic burden associated with ADHD among children and adolescents in the US in 2018. ***Methods:*** Excess costs (in 2018 US dollars) incurred by children and adolescents with ADHD were evaluated from a societal perspective. Direct healthcare costs were estimated using data from the Truven Health Analytics MarketScan® database (01/01/2013-12/31/2018). Direct healthcare costs, non-direct healthcare costs (i.e., research and training, education, substance use [adolescent only], and road traffic accidents [adolescents only]), and indirect costs (i.e., caregiving, unemployment [adolescent only], productivity loss [adolescent only], and premature mortality [adolescent only]) were assessed using academic and governmental publications. ***Results:*** Based on an estimated ADHD prevalence of 10.0% among children (N=2.9 million) and 6.5% among adolescents (N=1.7 million), total excess costs incurred by children and adolescents with ADHD were estimated at $19.4 billion ($6,799 per individual) and $13.8 billion ($8,349 per individual), respectively. Among children,

excess costs comprised $5.0 billion (25.9%) in direct healthcare costs, $11.7 billion (60.0%) in direct non-healthcare costs, and $2.7 billion (14.1%) in indirect costs (caregiving costs only). Among adolescents, excess costs comprised $4.0 billion (29.0%) in direct healthcare costs, $7.4 billion (53.5%) in direct non-healthcare costs, and $2.4 billion (17.5%) in indirect costs. Excess direct healthcare costs were mainly driven by pharmacy costs ($2.7 billion [54.3%] for children; $1.8 billion [44.9%] for adolescents). Excess direct non-healthcare costs were mainly driven by education costs ($11.6 billion [99.9%] for children; $6.7 billion [91.3%] for adolescents). Excess indirect costs were mainly driven by caregiving costs for adolescents ($1.6 billion [65.8%]). ***Conclusions:*** The economic burden of ADHD is substantial among children and adolescents and was mainly driven by excess costs in education and caregiving. These data further emphasize the need for new approaches to reduce the high burden of ADHD in these populations.

Emerging Methods in Economic Evaluation

EM1
WHEN ARE BREAKTHROUGH THERAPIES COST-EFFECTIVE?

Olchanski N,[1] Lin PJ,[1] Yeh D,[2] Kowal S,[3] Cohen JT[1]
[1]*Tufts Medical Center, Boston, MA, USA,* [2]*Genentech, South San Francisco, CA, USA,* [3]*Genentech, Alameda, CA, USA*

Objectives: The US Food and Drug Administration (FDA)-designated breakthrough therapies offer substantial potential to improve health outcomes, but it is unclear whether their health gains represent favorable value for money. ***Methods:*** Using the Tufts Medical Center Cost-Effectiveness (CE) Analysis Registry we: (1) summarized the cost-effectiveness of breakthrough therapies (BT), as measured by the cost-per-quality-adjusted-life-year (QALY) metric; (2) compared the cost-effectiveness of BT and non-breakthrough therapies (NBT) in the US; and (3) identified factors associated with BT cost-effectiveness, using logistic regression models with a range of value benchmarks ($50K-$150K/QALY). ***Results:*** Between 2013 and 2018, FDA approved 264 drugs, designating 84 (32%) as breakthrough therapies. We identified published US CE studies for 26% of BT drugs (48 studies, 227 CE ratios) and 23% of NBT drugs (60 studies, 96 CE ratios). Publications focused on hepatitis C (HepC) or other infectious diseases (38% of BT studies, 23% of NBT studies) and neoplasms (48% of BT studies, 11% of NBT studies). Median BT incremental costs and QALYs exceeded corresponding values for NBT ($29,231 vs. $20,263 and 0.7 vs. 0.2 QALYs, respectively), and CE ratios trended toward greater favorability for BT compared to NBT drugs (median values $38,000/QALY vs. $50,000/QALY, respectively). For BTs, HepC drugs had the most favorable CE ratios, as removing HepC studies increased the median CE ratio to more than $140,000 (with median $65,000 incremental cost and 0.61 QALYs gained). Further, BTs for new molecular entities (NME) had median CE ratios about 40% lower than non-NME BTs, reflecting their smaller incremental costs and greater QALY gains. ***Conclusions:*** Breakthrough drugs may confer greater health benefits than NBTs in terms of QALYs gained. However, nuances, such as target condition, NME, and choice of comparator greatly influence whether greater relative health gains represent favorable value for money.

EM2
ECONOMIC IMPACT OF COMPASSIONATE USE OF MEDICINES

Jommi C,[1] Pantellini F,[2] Stagi L,[2] Cavazza M[1]
[1]*Bocconi University, Milano, Italy,* [2]*Roche Spa, Monza (MI), Italy*

Objectives: The economic impact of clinical trials in the perspective of trial sites has been already investigated. Instead, there is no evidence on the economic net benefit of compassionate use programs for medicines (CUP). This research aims to fill the information gap, investigating the economic consequences of ten CUPs in Italy carried out from May 2015 to April 2020 in the hospitals' perspective. These programs concern five cancer medicines used in different disease settings and two drugs for neurological disorders ***Methods:*** Economic net benefit includes avoided costs for standard of care (SoC) the patient would have received if he/she has not joined the CUP and costs not covered by the pharmaceutical industry and sustained by the hospital hosting CUP. The latter include costs of adverse event (only severe sides effects generating hospitalisation and ascribed to medicines used in CUP), combination therapies and diagnostic procedures not covered by the sponsor. SoC costing relied on publicly available estimation. Adverse events and diagnostic procedures were retrieved from the CUP and monetized using the relevant fee for episode ***Results:*** 2246 patients were enrolled in the 10 CUP. The SoC mean cost per patient and the total cost ranged from €10743 - €18201 and €24.1 - €40.9 million respectively. The mean cost per patient covered by hospitals hosting CUP and was equal to €1803 (€4 million). The net economic benefit ranged from €20.1 to €36.9 million ***Conclusions:*** Despite its limitations this paper illustrates for the first time the net economic impact of CUP in the perspective of payers. Additional evaluations are ongoing to better understand the overall effects of CUP implementation, i.e. the economic value of the comparative benefit profile of medicines used in CUP versus the SoC, including potential effects on indirect costs

EM3
ROBUSTNESS OF EXTERNAL CONTROL ARM: WHEN TO USE THEM

Ladouceur M,[1] Colby C,[2] Okala S,[3] Yue B[4]
[1]*Evidera, Verdun, QC, Canada,* [2]*Evidera, Oakland, CA, USA,* [3]*Evidera, London, UK,* [4]*Evidera, Orlando, FL, USA*

Background: During the COVID-19 pandemic, many aspects of traditional clinical trials have been affected worldwide. Recruitment of patients and on-site visits have been challenging when not compromised. Many groups have turned to the possibility of replacing their randomized standard of care (SOC) arm with a real-world (RW) external control arm (ECA). Unlike randomized controlled trials (RCTs) that have international guidelines, the use of an ECA is not subject to any consensus. ***Objectives:*** The aim of this study is to guide the design of an ECA (when it is justified or recommended) from different context and data sources. ***Methods:*** We propose to summarize the evidence into a decisional matrix. We crossed popular data sources (RW data collected prospectively, RW data obtained from retrospective chart review, administrative or insurance data, and clinical trial data) with situations where the use of an ECA could be justified or beneficial (regulatory submission, health economics and outcomes research [HEOR] investigation, hypothesis generation). Our reflection was influenced by our consulting practice at Evidera and by United States Food and Drug Administration (FDA) guidelines on the use of RW data. We developed a framework that should help researchers to build a quality ECA. Building an ECA should be based on a clear research question that will inform: (1) design and data source(s) to be used; (2) selection of control that will limit biases; and (3) adjustment methods that allow fair comparison with the treated arm. ***Results:*** Good ECAs would have a clear and accepted SOC treatment (limited changes in medical practice), standardized variables and definitions, similar outcome evaluations, and validity of the variables. ***Conclusions:*** When it comes to ECA, there is no one size fits all solution. The ECA should not replace RCTs but be considered as a complement tool to provide additional evidence to medical research.

EM4
RECOMMENDATIONS FOR HANDLING UNCERTAINTY IN ECONOMIC EVALUATION: A TARGETED REVIEW OF PHARMACOECONOMIC GUIDELINES

Berdunov V,[1] Sammon C,[1] Ramagopalan S[2]
[1]*PHMR Ltd, London, UK,* [2]*F. Hoffmann-La Roche, Basel, BS, Switzerland*

Objectives: The appropriate handling of uncertainty is an essential element of economic evaluation of healthcare interventions. Accepted methods include deterministic and probabilistic analyses to characterise parametric uncertainty, and scenario analyses to test uncertainty propagated by methodological and structural assumptions. This targeted review examined which methods for handling uncertainty are recommended in pharmacoeconomic guidelines around the world. ***Methods:*** Pharmacoeconomic guidelines were identified from HTA agency websites, PubMed and Google Scholar, and manual searches of references from key publications. Inclusion criteria were open access, inclusion of recommendations for handling uncertainty and publication in a language accessible to the reviewers. Two reviewers extracted data on the guidelines' recommendation for the type of sensitivity analysis and use of technical tools (e.g. Tornado diagrams, scatter plots, CEAC). ***Results:*** Forty-three national or supranational pharmacoeconomic guidelines passed the inclusion criteria. One-way deterministic sensitivity analysis (DSA) was requested in thirty-five (81%) guidelines. Notable exceptions included CADTH (Canada), which recommended against the use of DSA, and HAS (France) which considered DSA of limited use compared to probabilistic methods. Probabilistic sensitivity analysis (PSA) was compulsory in twenty-nine (67%) guidelines and a further five (12%) included it as an optional analysis. Tornado diagrams were specified in fifteen (43%) guidelines which required a DSA. The most requested tools for reporting PSA were acceptability curves (56%) and scatterplots on the cost-effectiveness plane (44%). Value of information analysis based on PSA results was recommended in ten (29%) publications. Scenario analyses to examine the impact of structural assumptions were recommended in fourteen (33%) guidelines. ***Conclusions:*** Both deterministic and probabilistic methods for characterising uncertainty were endorsed by most published guidelines, with accepted tools such as Tornado diagrams, scatter diagrams and acceptability curves commonly requested. When planning global cost-effectiveness models, manufacturers should consider additional analyses required by