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?

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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

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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

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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

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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

some authorities, such as value-of-information analyses and scenario analyses for structural assumptions.

Hospital and Clinical Practice Studies

HP1
VALIDATED MODELS FOR PRE-TEST PROBABILITY OF STABLE CORONARY ARTERY DISEASE: A SYSTEMATIC REVIEW SUGGESTING HOW TO IMPROVE VALIDATION PROCEDURES

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Objectives: An overuse of invasive and non-invasive anatomical testing for the diagnosis of coronary artery disease (CAD) affects patients' and healthcare professionals' safety, and the sustainability of Healthcare Systems. Pre-test probability (PTP) models can be routinely used as gatekeeper for initial patient management. Several PTP models have been developed after the seminal work of Diamond and Forrester in the late 1970s, however to assess their generalizability to different populations extended validation procedures should be carried out and their results carefully analyzed. ***Methods:*** A systematic review has been carried out to assess the discrimination capabilities of PTP models validated on external populations. The main metric was the area under the ROC curve (AUC). A comprehensive search has been done in MEDLINE®, HealthSTAR, and Global Health databases on 22 April 2020. The review conforms to the PRISMA statement; protocol was registered in PROSPERO (CRD42019139388). ***Results:*** Nearly all the models considered in the 27 analysed papers include age, sex, and chest pain symptoms. Other common risk factors are smoking, hypertension, diabetes mellitus and dyslipidaemia. Only one model considers genetic profile. Reported AUCs range from 0.51 to 0.81. Relevant heterogeneity sources have been highlighted, such as the sample size, the presence of a PTP cut-off and the adoption of different definitions of CAD which can prevent comparisons of results and meta-analysis. Very few papers address a complete validation, making then impossible to understand the reasons why the model does not show a good discrimination capability on a different data set. ***Conclusions:*** We recommend a more clear statement of endpoints, their consistent measurement both in the derivation and validation phases, more comprehensive validation analyses and the enhancement of threshold validations of PTP to assess the effects of PTP on clinical management.

HP2
PATIENT-PROVIDER COST DISCUSSIONS AND OUT-OF-POCKET COSTS AMONG CANCER SURVIVORS WITH VARYING LEVELS OF CANCER-RELATED FINANCIAL HARDSHIPS

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Objectives: Previous research showed patient-provider cost discussions may reduce cancer survivors' out-of-pocket spending. Meanwhile, survivors who experienced cancer-related financial hardships may be more likely to have cost discussions. This study examined whether cost discussions and financial hardships were related to out-of-pocket spending. ***Methods:*** Using the 2016–2017 Medical Expenditure Panel Survey Experiences with Cancer Survey, survivors were classified as with or without a detailed discussion about out-of-pocket cancer care costs, based on self-reports. The relationship between detailed discussion and out-of-pocket costs was estimated using generalized linear models with gamma distribution and log link. Model 1 covariates included age, sex, race/ethnicity, marital status, education, employment, income, region, insurance, overall health, comorbidities, ≥1 cancers, time since cancer treatment, ambulatory visits, hospitalization, and survey year. Model 2 additionally adjusted for cancer-related financial hardship intensity (presence of material, behavioral, and psychological hardships, range: 0, 1, 2+). Model 3 additionally included an interaction term for cost discussion and hardship intensity. ***Results:*** Among 1,428 survivors included, 11.4% (95% CI: 9.1%–13.7%) had a detailed cost discussion. Having a detailed discussion was associated with significantly lower out-of-pocket costs ($1,041) compared to without a detailed discussion ($1,389) (average marginal effect [AME]=$347, 95% CI, –$610 to –$30) in model 1, which remains significant after controlling for financial hardship (model 2: AME=–$365, 95% CI, –$616 to –$57). In model 3, having a detailed discussion was significantly associated with lower costs only among no-hardship or multiple-hardship survivors (no hardship: AME=–$380, 95% CI, –$688 to –$11; multiple hardships: AME=–$659, 95% CI, –$1056 to –$156), but not among single-hardship survivors. ***Conclusions:*** Detailed cost discussions were associated with reduced out-of-pocket costs independent of financial hardship intensity, yet the reduction extent may vary by hardship intensity and warrants further investigation. Providers should continue to be encouraged to have detailed cost discussions with patients.

HP4
DOSE MEDICAID EXPANSION PROVIDE AFFORDABILITY OF HELATHCARE SERVICE FOR ASTHMA POPULATION

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Objectives: The purpose of this analysis is to estimate the impact of Medicaid expansion in 2014 on healthcare services among asthma patients. ***Methods:*** A retrospective cross-section study was conducted among asthma patients aged 26-64 years in the United States between 2007-2018 using the Medical Expenditure Panel Surveys. The total expenditure and utilization of healthcare services, including prescription drugs, emergency department (ED) visits, hospital inpatients stay, outpatient department visits, office-based medical provider visits, and home health visits, served as the outcome variables. The study sample included 9,564 adults identified as having asthma by Clinical Classifications Software (CCS) disease categorization scheme. We excluded individuals who were covered by Medicare. We estimated a difference-in-difference (DID) design compared two outcomes of patients under 138% federal poverty level (FPL) and upper 138% FPL before and after the Medicaid expansion. The expenditures of healthcare services were estimated by two-part model with logit in the first part and generalized linear model in the second part. The utilization was estimated by negative binomial regression. Other covariates were included to adjust potential confounding factors. Expenditures were inflated to 2018 US dollars as a common year by using the Medical Care component of the Gross Domestic Product (GDP) price index. Estimates were survey-weighted and adjusted for complex multi-stage sampling design. ***Results:*** A significant difference was found in asthma prescription drug expenditure and utilization. The DID estimates indicated that the Medicaid expansion increased expenditure by $344.39 ($p<0.001$) and utilization by 2.15 claims ($p<0.001$) for asthma population under 138% FPL after Medicaid expansion. Expenditures of outpatient department visits decreased by 65.9% ($p<0.01$) for asthma population under 138% FPL after Medicaid expansion. ***Conclusions:*** Medicaid expansion were benefit to asthma patients under 138% FPL, especially on prescription drug utilization.

Health Technology Assessment Studies

HT1
EFFECTS OF STAKEHOLDER ENGAGEMENT WITH ICER ON COST-EFFECTIVENESS OF NEW INTERVENTIONS: LESSONS LEARNED FROM A CRITICAL REVIEW OF EVALUATIONS FROM 2018 TO 2019

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Objectives: Since its foundation in 2006, the Institute for Clinical and Economic Review (ICER) has had increasing influence on drug pricing and reimbursement decisions in the US. Such decisions directly affect all stakeholders—insurers, providers, manufacturers, patients, and others—yet there is little synthesis of the effectiveness of engagements by stakeholders on ICER's assessment of the cost-effectiveness of new interventions. The objective of this study is to evaluate the effectiveness of stakeholder engagement approaches and inform stakeholders of their potential role in collaborating with ICER. ***Methods:*** ICER evaluations from 2018 (n=12) and 2019 (n=8) were systematically reviewed. Key characteristics were extracted from 172 letters with a total of 1,463 comments documenting interactions between ICER and all stakeholders. Stakeholder engagement approaches were analyzed in terms of their effectiveness indicated by ICER's modification of its original cost-effectiveness analysis. ***Results:*** 30% of reviewed letters and 5% of comments resulted in a change in ICER's base-case analysis (49 comments in 2018, 23 in 2019); nearly half of these comments included specific data or a published article to support the stakeholder's recommendations. Other common types of suggestions that resulted in analysis revisions included comments relating to inconsistent model inputs across treatments (12/49 in 2018, 5/23 in 2019), clinical validity (12/49 in 2018, 0/23 in 2019), and concerns based on patients' perspectives (1/49 in 2018, 5/23 in 2019). Although these comments led ICER to amend the analysis, the revisions rarely affected ICER's conclusion on the cost-effectiveness of evaluated