responsive to change particularly in oncology. Therefore the objective of this study was to determine the level of responsiveness of the EQ-5D in oncology. **METHODS:** A systematic review identified relevant articles reviewing responsiveness of the EQ-5D in adults (EMBASE, Medline). Effects sizes (ES) were calculated for the studies identified where not already reported. A meta-analysis was undertaken of the effect sizes: homogeneity of variance was assessed (fixed effects) and random effects models applied where there was significant heterogeneity. Responsiveness was also compared for improvement/deterioration in health status. Analyses were conducted in SPSS v18. **RESULTS:** Data were available from 12 studies (3 breast, 2 prostate, as well as ovarian, lung and renal cancers) each with EQ-5D data at a minimum of 2 time points leading to a total of 45 entries. The overall unweighted ES was -0.26 (95%CI: -0.31 to -0.21), however there was significant heterogeneity in terms of effect sizes ($Q(44) = 427.00$, $p<0.001$) which was accounted for using the random effects model ($Q(44) = 39.58$, $p>0.05$). The overall weighted effect size (ES) was -0.17 (95%CI: -0.33 to -0.01). The weighted ES for improvement was 0.08 (95%CI: -0.02 to 0.18), and -0.52 (95%CI: -0.64 to -0.41) for deterioration. **CONCLUSIONS:** There is considerable heterogeneity in the reported effect size of the EQ-5D. Responsiveness of the EQ-5D in oncology trials as measured by effect sizes is modest at best. The instrument appears to be more sensitive to deterioration in health status than to improvements. Further work will explore the ES of the EQ-5d in comparison with responsiveness of disease-specific measures and changes in health status.

CA2

THE BURDEN OF CAREGIVING IN CANCER: THE STATUS OF CLINICAL RESEARCH

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OBJECTIVES: The responsibility of caring for cancer patients, often suffering from a magnitude of health problems, can result in a considerable burden for their caregivers, both physically and psychologically. The objective of this study was to assess the status and extent of clinical research into the burden of caregiving for cancer patients. **METHODS:** ClinicalTrials.gov was searched for all cancer trials that considered caregiver burden, using a matrix of search terms such as 'carer', 'burden of care' or 'caregiver'. The impact of geographical location or cancer type on the proportion of trials assessing caregiver burden, the outcome measures used and the proportion of trials including caregiver burden as an outcome over time were investigated. **RESULTS:** From a total of 36,184 cancer-focused trials documented worldwide, 1,596 (4%) assessed caregiver burden. Outcome measures included caregiver quality of life (QoL), satisfaction with care and mood states. The impact of caregiver burden in cancer trials within different world regions varied, with the highest proportion of trials that considered caregiver burden located in Mexico (23%) and Asia (14-22%). Trials for five major cancer types (breast, lung, prostate, colorectal, liver) assessed caregiver burden at similar frequency (4-5%). Evaluation of completed trials demonstrated that the proportion of cancer trials considering caregiver burden increased from <1% between 1997-2001 to 7% after 2012. **CONCLUSIONS:** Fewer than 5% of all cancer trials documented worldwide have evaluated the impact of caregiver burden, although geographical variation does exist. The equal assessment of caregiver burden across cancer types may suggest that no single cancer type is considered to have a higher degree of caregiver burden. Interestingly, while the number of total cancer trials evaluating caregiver burden documented to date is relatively low, the incidence has increased over the last 15 years, suggesting that the growing importance of caregiver burden is being recognised.

CA3

EMA APPROVAL OF DRUGS ON THE BASIS OF PIVOTAL NON-COMPARATIVE PHASE II TRIAL DATA

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OBJECTIVES: The recent European Medicines Agency (EMA) approval of crizotinib has highlighted the potential for regulatory approval to be gained on the basis of pivotal non-comparative Phase II data. This research aims to determine the circumstances under which the EMA will approve submissions on this basis. **METHODS:** All publicly available European Public Assessment Reports (EPARs) were screened up to June 2013. Submissions that were based on pivotal Phase II data were identified and the acceptance decision, disease, and level of benefit were extracted. **RESULTS:** Eight drugs (bevacizumab, bortezomib, crizotinib, dasatinib, everolimus, gefitinib, imatinib, ofatumumab) across ten indications been submitted to the EMA on the basis of pivotal non-comparative Phase II data. All submissions were for entry indications except imatinib, which was also submitted for two further indications on this basis. All, except crizotinib, were for indications with no alternative therapies and all were for onology indications except everolimus which was for subependymal giant cell astrocytoma (SEGA). All, except crizotinib, were EMA designated orphan medical products for these indications. One submission was rejected (bevacizumab), one was restricted (ofatumumab), and eight were approved. Top-line supportive Phase III data was only available in two submissions (crizotinib and everolimus). Overall response rates (ORRs) were the primary endpoints in all submissions except imantinib and dasatinib in leukaemia indications and everolimus in SEGA. Rejected drugs had ORRs of 47% (ofatumumab, rejected subpopulation) and 38% (bevacizumab). Approved drugs had ORRs of 60% (crizotinib), 58% (ofatumumab, approved subpopulation), 40% (imatinib), and 35% (bortezomib). Despite low ORRs, imatinib was used to treat a disease with no licensed therapies (gastrointestinal stromal tumours), and bortezomib offered a 10% complete remission rate. **CONCLUSIONS:** Pivotal Phase II data can support EMA approval if it demonstrates substantial clinical benefits for small patient populations with severe diseases that lack therapeutic alternatives.

CA4

MEASURING THE COST OF LOST PRODUCTIVITY DUE TO PREMATURE CANCER-RELATED MORTALITY: A EUROPEAN OVERVIEW

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OBJECTIVES: To assess the economic burden of cancer by estimating years of potential productive life lost (YPPLL) and costs of lost productivity due to premature cancer-related mortality across Europe. **METHODS:** We derived the number of cancer deaths by sex for 23 of the most common cancer sites in 30 European countries from GLOBOCAN. YPPLL were calculated by multiplying the number of cancer-specific deaths for each productive age group (15-64) by standard life expectancy at the mid-point for each age group. Using the human capital approach, we multiplied standardised YPPLL for each individual by country- age- and gender-specific annual wages from age of death until retirement following adjustments for labour force participation and unemployment. Costs were expressed in 2008€. **RESULTS:** All cancer sites combined generated a total of €150.9 billion in premature mortality costs in Europe in 2008. Western Europe accounted for almost half of the total, followed by Northern (21%), Southern (21%) and Central & Eastern Europe (9%). Findings contrasted with YPPLL where Central & Eastern Europe had the highest burden. Male costs exceeded female costs by 88% in Europe as a whole (male: €98.4 billion; female: €52.5 billion) and across all European regions. Lung was the most expensive site (€34.7 billion; 23% of total costs), followed by breast cancer (€13.6 billion, 9%), colorectal cancer (€12.1 billion, 8%), brain & CNS (€9.1 billion, 6%) and pancreatic cancer (€7.5 billion, 5%). According to premature mortality cost per death, testicular cancer was the most expensive site (€2.5 million per death), followed by brain & CNS cancer (€481,512) and Hodgkin lymphoma (€474,559). **CONCLUSIONS:** Lost productivity costs due to cancer-related premature mortality are significant in Europe. Productivity costs provide an alternative perspective on the cancer burden on society and may inform cancer control policy decisions.

CONCEPTUAL PAPERS

CP1

INCREMENTAL COST PER QUALITY-ADJUSTED LIFE YEAR GAINED? THE NEED FOR ALTERNATIVE METHODS TO EVALUATE MEDICAL INTERVENTIONS FOR ULTRA-RARE DISORDERS

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OBJECTIVES: To critically appraise the problems posed by the systematic valuation of interventions for ultra-rare disorders using conventional health economic analysis methods. **METHODS:** An international group of clinical and health economic experts met in conjunction with the Annual European ISPOR Congress in Berlin/Germany, November 2012, to identify and deliberate underlying issues openly, adhering to the Chatham House rule. **RESULTS:** The group reached a broad consensus, including: The complexities of research and development new treatments for ultra-rare disorders (URDs) may require conditional approval and reimbursement policies, such as coverage with evidence development agreements, but should not be used as a justification for showing surrogate endpoint improvement only. As a prerequisite for value assessment, demonstration of a minimum significant clinical benefit should be expected within a reasonable timeframe. Regarding the economic evaluation of interventions for URDs, the currently prevailing logic of cost effectiveness (using benchmarks for the maximum allowable incremental cost per quality-adjusted year, QALY, gained) was considered inappropriate since it does not capture well-established social preferences regarding health care resource allocation. Such social preferences include, but are not limited to, a priority for care for the worse of (related to initial health state), for those with more urgent conditions (the so called "rule of rescue"), a relatively lower priority based upon capacity to benefit, and a dislike against "all or nothing" resource allocation decisions that might deprive certain groups of patients from any chance to access effective care. **CONCLUSIONS:** Alternative paradigms to establish the "value for money" conferred by interventions for URDs should be developed with high priority. Such methods should capture and reflect prominent societal value judgments, beyond efficiency as conventionally defined by QALY maximization under a budget constraint.

CP2

THE MULTIMODEL ENSEMBLE APPROACH TO REDUCING STRUCTURAL UNCERTAINTY IN DECISION ANALYTICAL MODELLING

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Decision analytical modelling represents an essential tool for undertaking health economic evaluation. Markov models provide a mathematical framework for such analyses, particularly in the context of assessing the cost-effectiveness of treatments for chronic diseases where economic outcomes are typically extrapolated beyond the duration of clinical trials. However, structural uncertainty is a key challenge, to methodologists and decision makers alike, that has hitherto attracted insufficient attention. Best practice guidelines advocate the testing of structural assumptions through alternative modelling approaches or conducting scenario analyses. It should be recognised, however, that structural differences in model design represent a strength, rather than limitation, of the modelling process and in fields such as climate modelling, multi-model comparisons and ensemble predictions have been used extensively as the basis for more robust policy decisions. Methods for combining models represents an emerging field in climate modelling, but the simplest approach is to treat all models equally and the mean of all model predictions has been shown to improve on the 'best' model predictions in numerous studies. A weighted multi-model approach may also be developed, but this remains an area of ongoing debate. To date, health economists have not fully embraced the potential of the multi-model paradigm to reduce structural uncertainty. In this work,