January 2015, compared with an estimated 20-30 patients diagnosed-per-year (estimated total uptake of 120-180 from recommendation). However, in some instances the number of patients treated with an HST were very low: zero patients for Strimvelis® (HST7), ≤10 for eliglustat (HST5), and ≤10 for metreleptin (HST14); much lower than any reported estimates in their respective HST appraisals (Strimvelis®: 3 diagnosed/year; eliglustat: 50-100 eligible patients; metreleptin: <200 eligible patients). Relatively few therapies have been recommended under the NICE HST pathway since 2015 compared to the standard NICE process with STA/MTA. Further, these recommendations have been over 19-months from EC-approval. Even following a positive NICE recommendation, several of these have not achieved meaningful patient access, potentially due to the lack of awareness for rare diseases, and likelihood of underdiagnoses.

## P39
## BETTER OUTCOMES AND VALUE FOR MONEY WITH COST-EFFECTIVENESS MODELLING OF CASCADE SCREENING STRATEGIES FOR FAMILIAL HYPERCHOLESTEROLAEMIA

**Faria R,**[1] Cox E,[1] Saramago P,[2] Haralambos K,[3] Watson M,[4] Humphries SE,[5] Qureshi N,[6] Woods B[7]
[1]*University of York, York, UK,* [2]*University of York, Heslington, York, UK,* [3]*University Hospital of Wales, Cardiff, UK,* [4]*University Hospital Southampton NHS Foundation Trust, Southampton, UK,* [5]*University College London, London, UK,* [6]*University of Nottingham, Nottingham, UK,* [7]*University of York, York, YOR, UK*

***Objectives:*** Cascade screening for familial hypercholesterolaemia (FH) refers to the systematic testing of relatives of people known to have FH (termed 'indexes'). Cascade screening is cost-effective compared to no screening, but alternative screening strategies have not been studied. Our objective was to identify the cost-effective strategy to select indexes to cascade, and to contacting and testing their relatives. ***Methods:*** We developed a new cost-effectiveness model informed with routinely collected UK data from indexes and their relatives. Our decision tree model takes the UK National Health Service perspective and calculates, per index assessed to the cascade, the relatives diagnosed, cascade costs, quality-adjusted life years (QALYs), healthcare costs and incremental cost-effectiveness ratios (ICERs). ***Results:*** We compared 1792 strategies. The cost-effectiveness frontier was mostly formed by strategies which contacted 1st and 2nd degree relatives of indexes with genetic FH simultaneously and directly. The cost-effective strategy diagnoses relatives according to whether they were on lipid lowering treatment, cholesterol, and age, with some having confirmatory genetic testing – it diagnoses 52% affected relatives, at a cascade cost of £536; ICER = £13,996/QALY. Sequential contact (i.e. contacting second degree relatives only when their first degree relative was diagnosed with FH), indirect contact via their index/relatives and genetically testing them diagnoses 36% of relatives, while direct and simultaneous contact with genetic testing diagnoses more relatives (56%); neither are in the cost-effectiveness frontier. If genetic testing is not available, cascade screening remains cost-effective, diagnosing 41% of relatives (ICER=£5,603 vs no cascade). Results are robust to alternative scenarios bar those affecting long-term benefits of diagnosis. ***Conclusions:*** Simultaneous and direct contact of relatives of indexes with genetic FH and a mixed approach to testing relatives is cost-effective and achieves better outcomes than sequential and indirect contact. Identifying this strategy required systematic comparison of multiple alternatives, which is only achievable with cost-effectiveness modelling.

## P40
## HTA AGENCIES PERSPECTIVE ON SURVIVAL MODELLING IN CELL OR GENE THERAPY APPRAISALS

**Lissdaniels J,**[1] Medin E[2]
[1]*Parexel International, Vällingby, Sweden,* [2]*Parexel International, Stockholm, Sweden*

***Objectives:*** The first cell- and gene therapies, so called advanced therapy medicinal products (ATMPs), have recently become available, making it possible to treat, and even potentially cure, very severe and sometimes previously untreatable conditions. These characteristics have led to a discussion among health economists about whether a specific methodological reference case is required for economic evaluation of gene therapies and the conclusion has been that a new methodological reference case is not required but that "the confluence of various characteristics can lead to specific methodological challenges...". Traditional survival modeling may underestimate outcomes by assuming the same mortality rate for all patients, in situations where the treatment could lead to the cure of a patients. Mixture cure models have been suggested as a supplementary analysis, alongside standard parametric models. The aim of this study was to review reimbursement appraisal reports of the 12 EMA approved ATMPs, to identify the differences in methods and assumptions in survival modelling of long-term treatment effects across different HTA agencies. ***Methods:*** Publicly available assessment reports were retrieved from each reimbursement agency's website in the Nordics, the Netherlands, England and Wales, Canada and Australia for the relevant drugs. ***Results:*** Across the HTA agencies different level of acceptance to non-standard survival modelling is seen. E.g. in appraisals of cell-therapies, mixture cure models have been accepted in the Nordic countries and in England and Wales but assumptions around the percentage of cured patients and the preferred source for the survival extrapolation post clinical trial follow-up differs. In appraisals of gene-therapies, the exploration of the impact of the main assumptions that drive model results have been recommended across the HTA agencies. ***Conclusions:*** There is yet not an established golden standard on how to apply survival modelling to ATPMs and the preferences on the methodology varies across HTA agencies.

# Methodological Developments in Network Meta-Analysis and Comparative Effectiveness Research

## P41
## CROSNMA: A NEW R PACKAGE TO SYNTHESIZE CROSS-DESIGN EVIDENCE AND CROSS-FORMAT DATA

**Hamza T,** Salanti G
*University of Bern, Bern, BE, Switzerland*

***Objectives:*** In network meta-analysis, we synthesize all relevant available evidence about health outcomes from competing treatments. That evidence might come from different study designs and in different formats: from non-randomized studies (NRS) or randomized controlled trials (RCT) as individual participant data (IPD) or as aggregate data (AD). To utilize all available evidence, we need a software that allows us to combine these different pieces of information accounting for their differences, e.g. RCTs have typically lower risk of bias than NRS. ***Methods:*** We integrate the three-level hierarchical model that combine IPD and AD with the following four models that incorporate both RCT and NRS evidence by (a) ignoring their differences in risk of bias (b) using NRS to construct discounted treatment effect priors (c,d) adjusting for the risk of bias in each study and controlling the contribution of high risk of bias information in two different ways. ***Results:*** We have implemented these models in a new R package, crosnma. This software allows us for conducting Bayesian network meta-analysis and meta-regression. Up to three study- or patient-level covariates can be also included, which may help explaining some of the heterogeneity and inconsistency across trials. The package runs a range of models with JAGS by generating the code automatically from user's input. ***Conclusions:*** crosnma is a new R package to conduct Bayesian network meta-analysis and meta-regression to synthesise cross-design evidence and cross-format data. We believe that this package will encourage the investigators to not discard any relevant evidence on their analysis. Authors are supported by the HTx-project. The HTx project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 825162

## P42
## COMPARISON OF ESTIMATION METHODS FOR SINGLE-ARM TRIALS IN RARE DISEASES WITH HISTORICAL CONTROL GROUPS

**Barlev A,**[1] Brookhart MA,[2] Xun P,[3] Thirumalai D,[3] Sadetsky N,[1] Suissa S[4]
[1]*Atara Biotherapeutics, South San Francisco, CA, USA,* [2]*Duke University, Durham, NC, USA,* [3]*Atara Biotherapeutics, Thousand Oaks, CA, USA,* [4]*McGill University and Jewish General Hospital, Montreal, QC, Canada*

***Objectives:*** Randomized controlled trials are the gold standard for estimating treatment effects. However, in rare diseases with high unmet need, single-arm trials are used when randomization of patients to placebo or standard of care is infeasible or unethical. We evaluated various methods to control for confounding in estimating treatment effects in a small single-arm trial with a historical comparator group. ***Methods:*** We used simulation to evaluate different techniques to estimate the "true" treatment effect on overall survival (OS) and objective response rate (ORR) in a specific target population using an external comparator design. We varied effect size, sample size, confounders, and correlation between confounders. We assessed two broad categories of methods: i) requiring specification for treatment allocation [propensity score (PS)-based inverse probability of treatment weighting (IPTW), standardized mortality/morbidity ratio (SMR), stabilized IPTW (SIPTW), overlap weighting (OW), stratification, and matching], and ii) adding outcome information (g-computation). Their precisions and accuracies were evaluated by a combination of 95% confidence interval (CI) coverage, power, bias, and mean square error (MSE). ***Results:*** G-computation resulted in the most accurate and precise estimator of OS (95% CI coverage: 93.5%, power: 69.3%, bias: -0.001, MSE: 0.055) in a small sample size scenario of 30 treated subjects compared with 120 comparator subjects. Similar results were observed for ORR. In comparison, results for OS were: 95% CI coverage: 72.8%, 65.6%; power: 75.9%, 62.6%; bias: -0.026, 0.072; MSE: 0.114, 0.167 for SMR and IPTW, respectively. ***Conclusions:*** In our simulated example, the g-computation estimator performed best to control confounding in a small single-arm trial with an external comparator group. PS based methods (e.g., SMR & IPTW) may be suitable as an initial step in the creation of the comparator arm when researchers are blind to the outcome, while g-computation can be subsequently used to estimate the efficacy of treatment.

## P43
## A CASE STUDY AND SIMULATION TO COMPARE DIFFERENT INDIRECT TREATMENT COMPARISON METHODS UNDER VARYING ACCESS TO INDIVIDUAL PATIENT DATA

Ayers D,[1] Cope S,[1] Phillippo DM,[2] Jansen JP,[3] **Park J,**[1] Yuan Y[4]
[1]*PRECISIONheor, Vancouver, BC, Canada,* [2]*University of Bristol, Bristol, BST, UK,* [3]*PRECISIONheor, San Anselmo, CA, USA,* [4]*Bristol-Myers Squibb, Princeton, NJ, USA*