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# Delays in publication of cost utility analyses conducted alongside clinical trials: registry analysis

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drafted the report. VBO'L, AMM, LCB, and OS did the genotyping. PNK and SM recruited some of the cases and PDM provided the Guthrie cards for the controls. LD did the statistical analysis. All authors contributed to writing revisions of the report and approved the final manuscript. PNK is guarantor.

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Competing interests: None declared.

Ethical approval: Research Ethics Committee of the Health Research Board. We got written informed consent from all participants.

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## Delays in publication of cost utility analyses conducted alongside clinical trials: registry analysis

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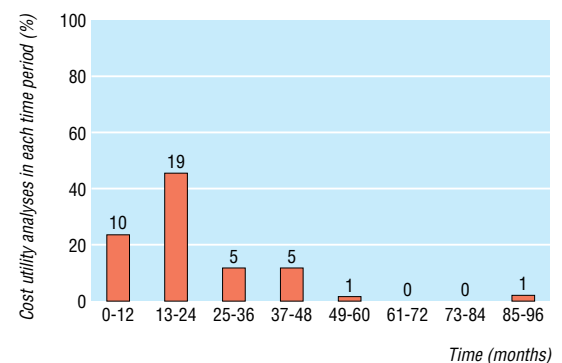
Economic evaluations conducted alongside randomised controlled trials enable analysis of detailed, patient level data on efficacy, cost, and quality of life in a controlled setting. They can provide timely and reliable assessments of value for money, to inform decisions on coverage and reimbursement.<sup>1-3</sup>

The *BMJ* recently decided to consider trial based economic evaluations for publication only if the clinical results are submitted to the journal as well.<sup>4</sup> We assessed the extent to which cost utility analyses are conducted alongside trials, estimated the time lag between the publication of trials' clinical and economic results, and compared the characteristics of journals publishing the clinical trial data and the cost utility analyses.

### Methods and results

We conducted a systematic search for original English language cost utility analyses published in 1976-2001 by using Medline and other electronic databases. Two readers independently reviewed each study and came to a consensus on whether the analysis was conducted alongside a trial (data on both efficacy and resource use from the trial were used for the analysis). We identified the journal and publication date for each cost utility analysis and the corresponding trial. To assess the study's potential readership and dissemination we used paired sample *t* tests to compare the mean impact factors of journals in which studies were published and the extent to which publications were subsequently cited by other authors.

Of 533 cost utility analyses identified, 45 (8%) were trial based economic evaluations and covered a variety of clinical areas, particularly cardiovascular disease, cancer, and psychiatry (a full list of studies is available at [www.hsph.harvard.edu/cearegistry](http://www.hsph.harvard.edu/cearegistry)). We could not determine the lag in publication between the trial and the economic evaluation for four studies, for which a specific trial could not be identified or trial results were



Time from publication of trial's clinical results to publication of economic results (n=41), showing number in each time period. More than 75% of cost utility analyses were published one year or more after publication of the trial's clinical results

published only in abstract form. In cases where the clinical trial results and economic evaluation were reported in the same article or in the same issue of the journal (n = 7), we assumed no lag.

On average, cost utility analyses were published almost two years after the publication of the corresponding trial (mean (SD) 1.8 (1.4) years; range 0-7.5 years) (figure). Journal impact factors were higher for trials than for cost utility analyses (11.0 *v* 4.9; *t* = -3.951 (df = 28); 95% confidence interval for the difference -9.25 to -2.93; *P* < 0.001). The mean number of citations per year (total number of citations divided by number of years since the study was published) was also higher for clinical trials than for the economic evaluations (27.4 *v* 3.4; *t* = -3.197 (df = 30); 95% confidence interval for the difference -39.24 to -8.64; *P* = 0.003).

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## Comment

We found a substantial delay in the publication of cost utility analyses, suggesting that reliable economic data are usually not available, at least in peer reviewed journals, for decision makers when decisions on adoption and reimbursement are typically made. Moreover, compared with trial results, dissemination of cost utility analyses takes place in journals with lower readership and influence. Several factors may contribute to this phenomenon: economic evaluations may be time consuming to construct, as they typically involve projections of trial data over time and across populations through use of modelling techniques and data from external sources; trial sponsors and investigators are eager to report important clinical results first, and more resources are initially allocated to interpreting and publishing these results; given that most readers of clinical journals are physicians, and not economists or policy makers, manuscripts presenting important clinical results are more often assigned by editors to an accelerated review and publication process.

Efforts have recently been made to keep the clinical and economic results of a trial together.<sup>4</sup> Further efforts (for example, fast track review process) should be made to promote timely dissemination of results of economic evaluations concurrent with or soon after the completion and publication of the trial.

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Contributors: DG had the original idea for the study, drafted the first version of the manuscript, did the statistical analysis, and is

### What is already known on this topic

To identify cost effective interventions, decision makers need timely and reliable information about the clinical and economic consequences of treatments

Economic evaluations conducted alongside clinical trials enable analysis of detailed, patient level data on efficacy, cost, and quality of life in a controlled setting

### What this study adds

A substantial delay in the publication of economic evaluations suggests that reliable economic data are usually not available when decisions have to be made

the guarantor. All authors extracted data, interpreted the findings, critically revised the report, and approved the final version.

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## DRUG POINTS

# Guillain-Barré syndrome seen in users of isotretinoin

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We report Guillain-Barré syndrome in people taking oral isotretinoin, a retinoid drug used in secondary care for severe acne.<sup>1</sup> The Committee on Safety of Medicines has received one other report of Guillain-Barré syndrome after oral isotretinoin (Committee on Safety of Medicines, private communication).

*Case 1*—A 31 year old man took 80 mg of oral isotretinoin a day for five weeks, during which he had epistaxis, dry lips, cough, and arthralgia before developing paraesthesiae in his feet and influenza-like symptoms. The next day he could not stand due to an areflexic tetraparesis and needed ventilatory support. Within four days he could only blink.

*Case 2*—A 13 year old boy took 50 mg of oral isotretinoin a day for two months, stopped for one week, and then took 30 mg a day for six weeks but had epistaxis, lethargy, and headaches. After stopping isotretinoin again for 10 days he developed a flaccid areflexic tetraparesis needing ventilatory support.

Both patients displayed cerebrospinal fluid albuminocytological dissociation. Nerve conduction studies in case 1 showed a motor axonal neuropathy with unrecordable sensory potentials and F waves, those in case 2, done after 21 months, showed borderline increased F wave latencies. Both patients received

intravenous immunoglobulin IVIg 2 g/kg and left hospital within three months. Neither patient has been rechallenged with oral isotretinoin, although the first continued to use topical isotretinoin gel 0.05% which is not absorbed.

Retinoids affect the development, differentiation, and function of the central nervous system. Sensory neuropathy has been described in patients taking the retinoid drug acitretin.<sup>2</sup> Over a 19 year period, an estimated 375 000 patients have been treated with oral isotretinoin in the United Kingdom (Roche, personal communication), and the annual incidence of Guillain-Barré syndrome is about 2 in 100 000. This is insufficient to establish a causal association between Guillain-Barré syndrome and isotretinoin. We hope to alert others to report similar cases.

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