Guest Editorial

Estimating medication costs for economic evaluation

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Introduction

Medications are a key component of care for many health conditions, consuming £15.5 billion of the National Health Service budget in England in 2014-15 (Health and Social Care Information Centre, 2015). Giving proper consideration to their role in treatment and treatment costs is thus an important aspect of assessing the cost-effectiveness of alternative approaches to care.

For the purposes of cost-effectiveness assessments at a national level in England, the National Institute for Health & Care Excellence (NICE) recommends the use of public list prices (or the Drug Tariff for medicines predominantly prescribed in primary care), including any negotiated discounts, in reference-case analyses presented for their consideration (NICE, 2013). However, the extent to which the detail of such price lists is utilised within economic evaluations is subject to variation, and decisions about if and how to account for medication costs may be complex due to the multiple dimensions to their costs: for example, research and development; production; distribution and storage; transaction costs including regulatory approval and price negotiations; user contributions to costs; and individual-level variations in use not only in terms of type of medication used, but also in terms of specific preparations, mode of administration, dosage, length and frequency of use, etc.

While there are now several methods guidelines and reporting standards for economic evaluations (e.g. Husereau et al., 2013), these largely refer to measuring and valuing resources in general, without any particular focus on medication costs. The most specific guidance is provided by the ISPOR Drug Cost Task Force Report (Hay et al., 2010), which set out to create drug costs standards from societal, managed care, US government, industry, and international perspectives. This highlights the importance of the perspective taken, since this determines the cost value assigned to medications, and details the need for: transparency in measurements and values; sensitivity analyses around the drug costs used; consideration of actual prices paid by payers; consideration of future trends in prices (particularly around the time that patents end); recommendations to be kept up to date in light of new information; consideration of medication adherence; consideration of user payments; standardised drug units; and context-specific costs.

It is unclear to what extent such nuances are considered in evaluations, and approaches to both measurement and valuation of medication range from individual-patient-level micro-costing approaches that aim to collect detailed information on medication use and apply unit costs which reflect individual-level variations, to macro-costing approaches, whereby some form of general or aggregate costs (such as an average prescription cost or a general prescription charge) are applied to medication use. The latter is naturally less time-consuming in terms of data collection and processing, but less accurately reflects differences in medication usage and costs between individuals. In part, such variations in approaches merely reflect context-specific judgements on the relevance of a micro-costing approach to the decision problem, but there can often be a lack of transparency surrounding such considerations.

The scope for methodological variations is naturally greater when conducting trial-based economic evaluations based on individual-level data rather than, for example, models based on over-arching assumptions applied across summary data. For other types of health care resources, it has been shown that divergent approaches to estimating costs can result in differences in cost estimates sufficiently large to influence funding decisions (Clement et al., 2009). It remains unclear whether this can also be the case when estimating medication costs. We thus recently examined the potential impact of alternative approaches to medication costing in a prospective trial-based economic evaluation of alternative medication strategies for treatment of rheumatoid arthritis (Patel et al., submitted; Heslin et al., 2017) and seek here to highlight the issues raised by that work.

Methods

The TACIT trial

The TACIT trial (Scott et al., 2015) examined alternative approaches for the treatment of established rheumatoid arthritis (RA), a common long-term inflammatory disorder that affects 0.5-1 per cent of adults in industrialised countries (Scott et al., 2010). It was an open-label, multicentre, randomised controlled trial conducted over 12 months, with patients recruited from 24 clinics across the UK. The trial was driven by economic questions arising from the availability of newer, and more expensive, medications (biological drugs such as Tumour Necrosis Factor inhibitors (TNFis)) which show promise of cost-effectiveness in the longer term but carry concerns about short-term cost-effectiveness (Losina & Katz, 2017) and affordability. The TACIT trial therefore compared a treatment strategy of starting treatment with TNFis or with combinations of the cheaper conventional Disease-Modifying Anti-Rheumatic Drugs (cDMARDs), with the option to switch treatments either way after a given period.

We assessed the costs of TNFi and cDMARDs ('trial medications'), plus costs of other concomitant prescribed medications ('non-trial medications'; any cause) as part of a comprehensive economic evaluation that assessed cost-effectiveness from both health and social care, and societal, perspectives. Trial medications for all 205 participants in the trial were recorded prospectively by clinicians for the entire year of follow-up, using specifically designed proformas; non-trial medication use was measured within an adapted version of the Client Service Receipt Inventory (CSRI) administered with participants at baseline, 6 months and 12 months. It requested retrospective participant self-reports of prescription medication use in terms of medication name, dose, frequency of use and number of days taken during the previous three months. For the purposes of the economic evaluation, all cost estimates from CSRI data relating to 3-month periods were doubled to extrapolate costs to 6-month periods so that cost estimates could be linked with outcomes data collected at 6 and 12 months. Participant follow-up rates were over 90 per cent for various components of the data, thus offering a detailed dataset and good opportunity to examine both micro and macro approaches to estimating medication costs.

Medication costing approaches

Since trial medications formed the core interventions of interest in this trial, we implicitly took a micro-costing approach to their cost estimation as recommended for interventions examined in an economic evaluation (Weinstein et al., 1996; Drummond et al., 2015) – this aspect of the study presented few feasibility issues because trial medications were limited to a handful of different medications. The more common and problematic situation in economic evaluations is when the number of medications used across all participants runs into tens or hundreds, requiring more care and time to collect data, collate unit costs and process data, including addressing the potentially multiple missing-data scenarios that could exist across the relevant variables. In this respect, handling data for the non-trial medications in the TACIT trial was more challenging, so we focused attention on these additional medications, rather than trial medications, for our comparison of alternative costing approaches.

We examined the impact on the trial results when taking four alternative medication costing approaches that have been used in previous economic evaluations, demonstrating the variability in approaches used. These are all detailed in Table 1 but can be summarised as follows: detailed micro-costing approach for all medications (base case); costing only medications used by at least 1.5 per cent of patients; costing medications based on their chemical name; and applying an average prescription cost rather than medication-specific cost. Table 1 also sets out the approaches we took to handle any associated missing data under each approach, and importantly illustrates another aspect of methodological variation when estimating medication costs.

We obtained medication unit costs from two very commonly-used resources. First, the British National Formulary (BNF) (Joint Formulary Committee, 2010) which provides key information and net ingredient costs for medications available from the NHS. Second, the NHS Prescription Cost Analysis (PCA) (Health & Social Care Information Centre, 2011) which provides information on national primary care prescription data dispensed in England, organised by the same therapeutic classes used in the BNF. The net ingredient cost (NIC) is the basic price of a drug, excluding Value Added Tax, as listed in national standard price lists. This is useful for comparative purposes but does not necessarily reflect any discounts negotiated by specific payers (Health and Social Care Information Centre, 2015). We applied costs of generic preparations (wherever

available) over branded versions to ensure cost estimations were conservative (although we acknowledge that for some medications this may have had the effect of under-estimating costs when more expensive branded preparations were used, and that for others costs may have been over-estimated since generic preparations may rarely be more expensive).

We examined the impact of these alternative approaches 2-4 by comparing resulting trial findings against those derived from the base case approach 1. We examined quantitative changes to estimates of mean total non-trial medication costs and mean total health and social care costs using (a) paired sample t-tests (confirmed by Wilcoxin Rank-Sum tests to account for non-normal distribution) and (b) overall agreement as measured using Lin's concordance correlation coefficient (CCC) and limits of agreement (Lawrence & Lin, 1989)). We also examined qualitative changes to the conclusions of the economic evaluation, as interpreted from incremental cost-effectiveness ratios based on comparisons of total health and social costs and health and quality of life outcomes between treatment arms. We held all other health and social care costs constant for these comparisons.

We limited our analysis samples to those cases which had relevant data for each analysis; of the 205 participants recruited, all (100%) had all CSRI data (and therefore non-trial medication data) available at baseline, 191 (93%) at 6 months, and 188 (92%) at 12 months. The sample used in the comparison of incremental cost-effectiveness ratios was limited to 186 (91%) due to missing outcomes data. All costs are reported in £ sterling at 2010/11 prices. Data were analysed using STATA 11 (StataCorp LP, 2011).

Results

The different costing approaches naturally led to different estimates of non-trial medication costs (Table 2):

Mean at baseline: £172, £144, £132 and £133 based on approaches 1, 2, 3 and 4 respectively.

Mean at 6 months: £95, £63, £89 and £99 based on approaches 1, 2, 3 and 4 respectively.

Mean at 12 months: £236, £200, £127 and £101 for approaches 1, 2, 3 and 4 respectively.

In comparing estimates obtained by costing approaches 1 and 2, there was good agreement in non-trial medication costs, and excellent agreement in total health and social care costs. Approaches 3 and 4 had poor agreement with approach 1 on non-trial medication costs but good agreement on total health and social care costs. Moving from approach 1 to approaches 2, 3 and 4 resulted in a progressively narrower distribution of medication costs across the sample, given that applying general costs per prescription item imposes a cap on costs. Of note, the different approaches had little impact on total health and social care costs, with non-trial medication costs constituting 11-13 per cent, 2-3 per cent and 3-6 per cent of total mean health and social care costs at baseline, 6 months and 12 months respectively. Given such small contributions to total care costs in this sample, the small variations in non-trial medication costs under the different costing approaches had negligible impact on the trial's cost-effectiveness conclusions (Heslin et al., in press).

Discussion

While our analysis shows that alternative approaches to costing medications have no impact on the conclusions of the TACIT trial due to the small contribution of non-trial medication costs to total care costs, there were nevertheless notable effects on the estimates of medication costs; such differences, and their consequences for decision-making, could be more pronounced for other treatments/patient groups for which medications are a dominant constituent of care.

Usefully, we have demonstrated that approach 2 – estimating costs for only those medications used by at least 1.5 per cent of the sample – provides similar estimates to a gold-standard micro-costing approach. This could thus offer a lower-effort methodological alternative when necessary, although it does risk excluding high-cost medications that might be used by only a few participants but may potentially cost more than the total costs of more commonly-used low-cost medications. Our results also suggest that the more macro-costing approaches 3 and 4 may be inappropriate if a particular patient group is likely to make use of high-cost medications, since the loss of detail could potentially lead to a significant under-estimation of care costs. Conversely, where medication costs are a small component of care, macro-costing approaches could alleviate some of the data collection and analysis burden without impacting on results, although the importance of estimating these costs at all then needs further consideration. Overall, the results demonstrate a need for greater attention

to medication costing in economic evaluations, including greater emphases on early-stage work to explore the importance of medication costs to the decision problem and the ability to collate necessary data reliably.

There are, of course, caveats to these interpretations, the main being that similar comparisons for other patient populations and areas of care may suggest different conclusions about the relative impacts of different approaches. Also, we collected medication use data every six months but, to minimise risks of recall bias, restricted participants' retrospective reports to only the previous three months. This then necessitated data extrapolations to estimate medication costs for the intervening periods that lacked data, and our simple approach to extrapolation may not accurately reflect medication usage for those intervening periods. Finally, we have not covered here some of the broader contextual issues that contribute further challenges for accurate estimation of medication costs. For example:

Standardised price lists based on net ingredient costs are convenient and commonly-used unit cost sources, but true economic costs, or even prices actually paid, can deviate from these. For example, the NICE guide to methods of technology appraisal (NICE, 2013) notes that price reductions, such as those available through patient access schemes, may be associated with further costs which should be accounted for to reflect true costs (NICE, 2013; paragraph 5.5.2). While the proprietary, confidential and localised nature of some medication purchasing contracts may prevent access to relevant information, NICE (2013) specifies that "The Commercial Medicines Unit publishes information on the prices paid for some generic drugs by NHS trusts...Analyses based on price reductions for the NHS will only be considered when the reduced prices are transparent and consistently available across the NHS, and if the period for which the specified price is available is guaranteed." (NICE, 2013; paragraph 5.5.2)

User prescription charges may partially offset some costs, but accounting for these presents yet further complexities.

Recent interest and challenges in operationalising a value-based pricing approach to medications (Sussex et al., 2013), under which prices are set and adjusted according to value based on patient outcomes, would potentially present even greater uncertainty about what cost values should be used in economic evaluations.

Conclusions

As for all potential resource items to include in an economic evaluation, a well-informed judgement is required to determine the importance of medication costs to a decision question to inform the level of attention to give to their measurement and valuation in an economic evaluation (Drummond et al., 2015). Where medications make up a small proportion of total costs, macro-costing approaches are unlikely to lead to any biases in cost effectiveness results, and thus may not require the additional analytical effort associated with micro-costing approaches. If a micro-costing approach is deemed appropriate, our analyses demonstrate the extensive need for (1) reliably accurate details on medication usage (name, dose, mode of administration, length of use, etc.); (2) assumptions for the calculation of medication unit costs even when detailed cost information (e.g. from the BNF, PCA or Drug Tariff) is available; and (3) specific strategies for handling any missing details. Much of this requires particular attention right at the design, rather than analysis, stage to establish feasibility and strategies for collecting sufficiently reliable and complete data.

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Table 1: Details of the four costing approaches applied to non-trial medications in the TACIT trial

Costing approaches	Approach to estimating costs of prescribed medications	Protocol for handling partially missing medication data

Approach 1: Cost per milligram (base case against which other approaches are compared)
This gold-standard micro-costing approach (Drummond et al., 2015) was used for the economic evaluation in the TACIT trial. The protocol for costing was determined prior to analyses.
	• Unit cost calculated per milligram (mg) based on most efficient pack size.
	  ○ Based on recommended dose in the BNF, choosing rheumatoid arthritis-relevant recommended doses where available.
	  ○ Maintenance prices chosen.
	  ○ Generic prices chosen.
	• Unit cost per mg applied to individual-level data according to dose, number of doses taken per day, and number of days taken during follow-up period.
	  ○ Used route/preparation stated by patient.
	  ○ For all creams/ointments, assumed 1 tube lasts a month and use the smallest tube.
	  ○ For dual medications, if both doses were in mg, we added them together. If one dose was in mg but the other was in micrograms, we only counted the mg.
		• If medication name was missing but other information was available: applied average prescription costs reported in PCA data.
		• If unit was missing but medication name was available: applied cost based on lowest cost chemical name for that medication from PCA; or based on PCA item cost where chemical name was unavailable.
		• If medication dose was missing: applied the PCA average cost for that medication, assuming each prescription lasts 1 month or use average item cost if specific medication not available.
		• If route/preparation was missing: applied what seemed most appropriate based on dose, but prioritised tablets and capsules.
		• If number of days used medication was missing: used a PCA item cost and assumed patient obtained the item once in that period.
		• If frequency was 'as necessary': number of days used in each period were missing so applied a PCA cost for that medication and assumed one prescription was obtained during each follow-up period.

Approach 2: Focusing only on medications used by at least 1.5 per cent of sample This involved the same micro-costing approach as for approach 1 but with an emphasis on the more commonly-used non-trial medications across the sample. Previously deployed as a practical approach: for example, by McCrone et al. (2011) for a study in which service users recorded approximately 1000 medication names. Costs are estimated for only those medications used by at least 1.5% of the sample.	• Micro-costing only undertaken for medications used by >1.5 per cent of sample. • Approach to unit cost estimation and application as per approach 1.	As per approach 1 except that, for obvious reasons, medication resource use with missing medication name was ignored.

Approach 3: Estimating unit costs according to chemical (rather than brand) name
The third approach, as previously used by Powell et al. (2013), involves estimating costs of all medications, but calculating unit costs differently. Unit costs were calculated for each medication by looking up the cost of a prescription for that medication's chemical name, according to the PCA.
	• Unit cost calculated according to PCA cost per item based on chemical name as recorded in BNF.
	  ○ Where there were different costs attached to the chemical names, we took a weighted average.
	  ○ Assumed any PCA cost is 1 month's worth of medication.
	• Number of PCA item costs assigned to each medication was based on the number of days of use reported by the patient. E.g. if patient took a medication for ≤ 30 days, we took this to indicate one prescription and thus applied one prescription item cost. Accordingly, we applied 2 prescription item costs for 31-60 days' use and 3 for 61-90 days' use.
		• If medication brand was needed but was unspecified and there were multiple chemical name options in the PCA: applied a weighted average.
		• If medication name was missing but other information was available: applied average PCA item cost.
		• If unit was missing but medication name was available: applied cost based on lowest cost chemical name for that medication from PCA; or based on average PCA item cost where chemical name was unavailable.
		• If number of days used medication was missing: assumed patient obtained the item once in that time period.
		• If frequency was 'as necessary': number of days used in each period was missing so assumed one prescription was obtained during each follow-up period.

Approach 4: Prescription cost analysis The final approach, which we have used in another trial-based economic evaluation (Ismail et al., submitted), is the most macro approach we examined.	• Unit cost was calculated as the net ingredient cost average for all medications listed in the PCA (£9.16). • Number of PCA item costs assigned to each medication was as per approach 3.	• If number of days medication was used was missing: assumed patient obtained the item once in that time period. • If frequency was 'as necessary': number of days used in each period was missing so assumed one prescription was obtained during each follow-up period.

Table 2: Mean cost estimates and comparisons from the alternative medication costing approaches applied in the TACIT trial*

	Mean cost (SD) (£, for 3 months)		Mean difference	95% Confidence interval for difference	Paired sample t-test	Correlation Concordance Coefficient**	95% Limits of agreement
	Approach 1	**Approach 2**					
Prescribed medications (over 3 months)							
Baseline (n=205)	172 (211)	144 (167)	28	12, 43	3.521, P< 0.001	0.815	-249, 194
6 months*** (n=191)	95 (226)	63 (176)	33	16, 49	3.962, P< 0.001	0.819	-264, 199
12 months (n=188)	236 (898)	200 (891)	35	18, 53	3.907, P<0.001	0.989	-290, 219
Health & social care (over 6 months, including trial medication)							
Baseline (n=205)	1335 (1665)	1279 (1639)	56	24, 87	3.521, P< 0.001	0.990	-499, 388
6 months (n=191)	3417 (2570)	3348 (2542)	69	35, 104	3.925, P< 0.001	0.995	-548, 410
12 months (n=188)	3781 (2798)	3705 (2788)	76	37, 115	3.829, P< 0.001	0.995	-606, 455
	Approach 1	**Approach 3**					
Prescribed medications (over 3 months)							
Baseline (n=205)	172 (211)	132 (120)	40	17, 63	3.453, P< 0.001	0.520	-365, 285
6 months*** (n=191)	95 (226)	89 (158)	7	-14, 28	0.647, P= 0.518	0.700	-303, 290
12 months (n=188)	236 (898)	127 (265)	108	-3, 220	1.913, P= 0.057	0.246	-1699, 1482
Health & social care (over 6 months, including trial medication)							
Baseline (n=205)	1335 (1665)	1255 (1644)	80	34, 125	3.453, P< 0.001	0.979	-729, 569
6 months (n=191)	3417 (2570)	3403 (2623)	14	-31, 59	0.615, P= 0.539	0.993	-628, 600
12 months (n=188)	3781 (2798)	3544 (2300)	236	-7, 480	1.914, P= 0.057	0.778	-3556, 3083
	Approach 1	**Approach 4**					
Prescribed medications (over 3 months)							

Baseline (n=205)	172 (211)	133 (85)	39	13, 64	3.0122, P= 0.003	0.333	-400, 322
6 months*** (n=191)	95 (226)	99 (85)	-3	-32, 25	-0.234, P= 0.815	0.258	405, 412
12 months (n=188)	236 (898)	101 (85)	135	13, 257	2.179, P= 0.031	0.033	-1873, 1603
Health & social care (over 6 months, including trial medication)							
Baseline (n=205)	1335 (1665)	1257 (1645)	78	27, 128	3.0122, P= 0.003	0.974	-800, 645
6 months (n=191)	3417 (2570)	3423 (2573)	-6	-67, 56	-0.185, P= 0.854	0.986	-841, 852
12 months (n=188)	3781 (2798)	3484 (2247)	297	31, 563	2.202, P= 0.029	0.729	-3923, 3329

*Intervention and control arms combined for the purpose of comparing estimates from the alternative approaches

**CCC of 1 indicates perfect agreement and –1 indicates perfect inverse agreement; less than 70 per cent agreement is poor, 70-79 per cent is fair, 80-89 per cent is good and 90- 100 per cent is excellent (Ciccheti, 2001).

*** 6 month figures are broadly lower for all approaches as a result of the medication strategies examined in the trial.