Being more economic with the collection of cost data in clinical trials

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Abstract

It has become common practice in economic evaluations conducted within randomised controlled trials (RCTs) to include a wide range of non-program costs in addition to the costs directly attributable to interventions under evaluation. This inclusive approach to the collection and analysis of cost data is intuitively appealing as it appears comprehensive, detailed and rigorous. In addition, an inclusive approach should also insure against the omission of important unexpected impacts of the intervention on resource use, whether positive or negative. It could also be argued, however, that the trend to a comprehensive collection and analysis of non-program cost data has added little or no value to economic evaluations. The inclusion of large amounts of sometimes irrelevant cost data is burdensome on patients, aggravates the problem of missing data endemic in cost data, potentially confounds analyses with random variation, and is an inefficient use of scarce research resources. These problems will be illustrated using recently published RCTs in the NIHR Health Technology Assessment program. The inclusion of non-program related costs was found to make no difference or contributed additional random variation to point estimates of mean costs in most studies. A sharper focus on relevant intervention-related resource use could improve the quality of economic evaluations conducted within RCTs and at a lower cost.

Background

Identification of resource use items for inclusion in economic evaluations is the first stage in planning an evaluation of cost-effectiveness within a clinical trial. A narrow evaluative approach focuses on the health care resources consumed to deliver a health care program including any changes to practice due to the new intervention and other direct consequences such as adverse events (Drummond, Sculpher et al. 2005). Program costs such as labour, medications, consumables, facilities and equipment are usually described in clinical protocols or guidelines and program-related resource use within a trial can usually be measured using clinical or research records. A narrow costing approach is sometimes found in evaluations of surgical interventions where the very high short term costs of both the surgery or alternative surgeries or the cost of inaction often overwhelm other considerations. While a narrow focus may be relatively straightforward compared to taking a broader perspective and possibly more precise, such an approach limits the generalisability of findings, and runs the risk that important non-program specific cost differences will be missed.

The advantages of a comprehensive approach to identifying health and social care costs over a narrow focus on program-related costs appears compelling. If such data are readily available then it might be considered a 'no brainer' to include all health service use wherever possible, if only as insurance against missing unexpected cost differences in the analysis and criticism that cost differences could have been offset by unmeasured changes in other service use (Glick, Doshi et al. 2007). A comprehensive approach also avoids problems of attribution of changes in resource use and costs to the interventions in question. Findings based on comprehensive resource use data will

also be more generalizable to other perspectives and settings than findings limited to direct program costs only.

It may seem a relatively costless choice to include all resource use data available from administrative databases, or better still data linkage across multiple datasets. However, the decision to collect and analyse even readily available or easily collected cost data is by no means costless. Costs include the administrative resources needed to collect, enter and store data, the burden on patients to report these data, and the health economic resources needed to analyse these data. The burden to patients caused by large numbers of detailed resource use items in a large scale clinical trial with multiple follow up points may be a contributing factor to unacceptably high levels of missing cost data reported in many studies. The reduction in sample size to subjects with complete cost and outcome data further compromises the validity of analyses of cost effectiveness. Recommended methods of handling missing data, such as multiple imputation, artificially reduce variation by imputing missing values from the observed data. There may be a further danger of bias random variation in high-value services of limited or no relevance could dominate results thereby masking the true impact of the intervention under evaluation (Johnston, Buxton et al. 1999). Ultimately these problems can lead to a loss of intelligibility and credibility of the results of cost effectiveness studies for decision makers.

In 1999 Johnston and colleagues (Johnston, Buxton et al. 1999) presented a comprehensive review of methodological issues concerning the collection of resource use data in clinical trials. With respect to the inclusion of resource use categories, they found seven factors were influential. These were economic theory, perspective, evaluation type, double counting risk, quantitative importance, attribution and study time horizon. Their report concluded that the collection of detailed patient-level resource use data may not be necessary and recommended approaches based on key cost-generating events and between-group differences. They outlined a systematic approach which assessed the relevance of resource use items based on their contribution to total costs and variability. On this basis, they found that resources that represent 1-4% of total costs, were of low frequency or had low unit cost could be safely ignored in analyses. This work was informed by earlier work by Knapp and Beecham, 1993 (Knapp and Beecham 1993) who coined the term 'reduced list costing' to describe an approach that focussed on major resource use items or drivers. Using this approach they suggested that items accounting for between 6 and 9% of total costs could be safely excluded from analyses.

It is fair to say, however, that 'reduced list costing' approaches have not been widely taken up in practice. While such an approach may be well suited to chronic and severe treatment populations dominated by high cost services, such as anorexia nervosa where hospital costs have been shown to dominate all other health and social services (Byford et al, 2007), reduced list costing may not be applicable in more acute conditions, such as depression (Knapp and Beecham 1993). The approach described by Johnston and colleagues also depends on detailed and up to date cost data from registries or pilot studies which are not necessarily available to investigators planning trials, making it difficult to assess in advance which resources are the dominant ones. Another limitation is that reduced list costing excludes resource use items based on their contribution to total costs rather than their impact on between-group differences, thereby potentially excluding items relevant in an economic evaluation.

More than a decade after the Johnston review, it may be timely to reflect on the type of resource use data that is being collected in contemporary economic evaluations in the UK. The aims of this review are to determine which approaches to resource use identification have been used in recent UK health technology assessments, to determine the impact of including non-program costs on point estimates of cost differences, and to assess the extent to which missing cost data has been influenced by the approach to cost identification. In order to obtain a representative, manageable and comparable empirical basis to address these questions, all within-trial economic evaluations reported in the NIHR Health Technology Assessment journal in 2012/2013 were included in the review.

Method

All randomised controlled trials (RCTs) in the NIHR Health Technology Assessment journal (http://www.journalslibrary.nihr.ac.uk/hta) published in 2012 and 2013 were reviewed and those that reported both effectiveness and cost effectiveness results were included.

In order to interpret these disparate data in a meaningful and coherent fashion, we extracted data from each study on between group differences in program costs (i.e. intervention costs as reported by the authors) and non-program costs. Non-program costs included all other cost items such as other health and social care costs, patient costs and productivity losses. Differences in costs are reported after adjustment for baseline costs if undertaken by the authors. We also identify and compare the proportion of missing data for costs, economic measures of outcome (quality adjusted life years; QALYs) and for clinical measures of outcome, where reported.

Results

Table 1 about here

Twenty cost-effectiveness analyses (CEA) were published alongside RCTs the Health Technology Assessment journal in 2012/13 (Table 1). Eleven evaluated mainly low-cost behavioural therapies, five involved high-cost surgical interventions and four evaluated medications. Nine concluded the interventions were not cost effective, three found limited evidence of cost effectiveness, two were inconclusive, and five were probably cost effective. Eighteen CEAs included non-program resource use and costs. Two high-cost surgical intervention (Brown, Powell et al. 2012, Pickard, Lam et al. 2012) studies collected non-program costs but did not ultimately include these in their analyses. One of these did not analyse non-program costs claiming they were driven by hospital stays caused by conditions unrelated to the technology in question (Pickard, Lam et al. 2012).

Differences in non-program costs were evident in 16 studies. Only two studies attributed these differences to possible between-group effects. One was an example of unexpected resource use (Banerjee, Hellier et al. 2013). The authors of this study speculated that an unexpected lower usage of unpaid informal care may have been due to the sedating effects of one of the drugs used to treat depression in dementia patients (Banerjee, Hellier et al. 2013). Russell et al reported hospital inpatient days were considerably shorter in cancer patients managed using a novel ultrasound technology to identify tumours (Russell, Edwards et al. 2013). Non-program costs in this study were limited to secondary care resources and hospital drugs but these could also be considered consequences of the intervention and therefore program costs.

Three studies attributed differences in non-program costs to bias due to outliers (Woods, Bruce et al. 2012, Molassiotis, Russell et al. 2013, Salisbury, Foster et al. 2013). Differences were dismissed as statistically insignificant in six studies (Bowen, Hesketh et al. 2012, Crawford, Killaspy et al. 2012, Forster, Dickerson et al. 2013, Powell, Kolamunnage-Dona et al. 2013, Underwood, Lamb et al. 2013, Watson, Crosby et al. 2013), and three studies did not offer any reasons for observed non-program cost differences (Gates, Perkins et al. 2013, Lenney, McKay et al. 2013, Stallard, Phillips et al. 2013). Finally, Chalder et al reported 'unaccountably' large differences in productivity losses in favour of control patients in a study of exercise for depression. These data were not subsequently incorporated into any cost-effectiveness analysis (Chalder, Wiles et al. 2012).

In ten studies differences in non-program costs were greater than differences in program costs and in the opposite direction (Bowen, Hesketh et al. 2012, Crawford, Killaspy et al. 2012, Banerjee, Hellier et al. 2013, Forster, Dickerson et al. 2013, Lenney, McKay et al. 2013, Molassiotis, Russell et al. 2013, Powell, Kolamunnage-Dona et al. 2013, Russell, Edwards et al. 2013, Salisbury, Foster et al. 2013, Watson, Crosby et al. 2013). Despite the potential decision changing consequences of these differences, five out of ten studies dismissed between group differences in non-program costs as statistically insignificant, two attributed the differences to outliers, and one offered no explanation. All studies included the non-program resource use costs in the cost effectiveness analysis.

Table 2 about here

The rates of missing cost data, reported in 16 studies, ranged from 20% to 64% (Table 2) consistent with previous reviews in the area (Noble, Hollingworth et al. 2012). In ten studies, levels of missing cost and QALY data were similar suggesting these data were collected together. Only four studies had similar levels of missing data for costs and primary clinical outcomes, suggesting these data were collected separately or reflecting the greater effort put into primary clinical outcomes compared to secondary outcomes. In the trials that reported missing cost data, cost data were missing for 4,315 out of 11,495 patients (37.5%) compared to 2,694 (23.5%) missing primary clinical outcome data. There was insufficient information to distinguish missing data due to missing items (i.e. a question left blank in a questionnaire) or entirely missing questionnaires (i.e. clinical records had not been accessed, the patient had not been interviewed or the patient did not complete the resource use section of the interview schedule). No studies reported missing data separated by program and non-program costs, although two studies specifically reported that missing data were mainly due to missing non-program cost items (Bowen, Hesketh et al. 2012, Brown, Powell et al. 2012). In addition, there did not appear to be any difference in the level of missing data between studies that collected comprehensive resource use and those that were limited to program costs.

Discussion

Most studies included in this review (18/20) collected both program costs and non-program costs, although only sixteen went on to use non-program cost data in their analyses. Only three studies attributed differences in non-program costs to differences between treatments. For the remainder, the considerable variation introduced by non-program related costs is largely unexplained and may be entirely random. In many studies, relatively small program costs appeared to have been swamped by random variation in larger scale non-program costs such as hospital care or productivity

losses. These results suggest that in a number of the studies, the inclusion of non-program related resource use may simply have added 'noise', disguising the true and economically meaningful impact of new interventions on resource use and costs.

Of the sixteen studies that reported missing cost data, nine had rates at or above 40%. We could not test the hypothesis that inclusion of non-program resource use contributed to elevated rates of missing costs data compared to outcome data because there were too few studies that only collected program costs and none of the studies that recorded both program and non-program costs reported missing data disaggregated by cost category. However, two studies reported that missing data were mainly due to missing non-program cost items, consistent with limited evidence that missing data increases as a study's perspective widens (Noble, Hollingworth et al. 2012).

Previous approaches to identifying relevant resource use in trial-based economic evaluations, such as reduced list costing, tended to focus on quantitative and statistical considerations rather than the relevance of resources to economic questions of value for money. Statistical inferences around mean costs can be misleading due to the skewed nature of cost data and underpowered sample sizes. These statistical issues are compounded when economically important differences are overwhelmed or disguised through the aggregation of relevant and irrelevant costs. A focus on major cost drivers in a condition or resources relevant to a particular analytical perspective will also be misleading if the treatments in question have little or no direct effect on them. Conversely, low-cost resources, such as specific medications, will be relevant if usage is changed by a new intervention, or the treatment population is large, or if effect sizes are small.

The relevance of resource use in an economic evaluation will not depend on statistical inference, the analytical perspective or quantitative importance. The test for economic relevance should instead be guided by the economic principles of marginal analysis and opportunity cost. Assessments of value for money are based on a comparison of differences in costs and differences in outcomes between alternative interventions. The resources relevant to such comparisons are those that will be consumed or saved by the alternative intervention within the time frame of the RCT. Relevant resources will include program costs, the direct consequences for practice and other direct consequences such as side effects (Drummond, Sculpher et al. 2005). Non-program costs will only be economically relevant if there is an *a priori* justification that an intervention will have a direct impact on resource use costs such as the costs of crime in drug addiction populations (Byford, Barrett et al. 2013) or formal and informal home care in dementia (Banerjee, Hellier et al. 2013).

The inclusion of non-program related costs should be justified *a priori* by their potential contribution to marginal costs. This justification can be based on a range of sources including clinical opinion, trial protocols, clinical guidelines and previous literature. For example, adverse event registers in an RCT can be used to identify intervention and condition related hospitalisations thereby reducing the risk that non-intervention related admissions or those due to rare or catastrophic events that have no bearing at all on the question of relative cost effectiveness of specific treatments will randomly alter the results of cost-effectiveness analyses. The economic literature is no longer as sparse as it once was, and health economists should carefully review the results of previous economic studies. This approach will still run the risk of missing unexpected non-program resource use and errors of misattribution, but such risks need to be weighed against the potential for confounding identified in this review.

The present review found many examples of low cost, low risk behavioural interventions where cost differences appeared to be overwhelmed by random variation in large scale cost drivers such as hospital costs and productivity losses. Health economists should temper the enthusiasm of clinical and research colleagues and confirm whether between-group differences can reasonably be expected in high cost resource categories with multiple cost drivers such as health care (comorbidities, patient preferences, patient lifestyles), productivity (education, geographical location, economic climate, co-morbidities), informal care (marital status, family composition), or service user expenditure (income) and explicitly warn of the risk of confounding of analyses by random variation from unobserved variables. In some studies the opportunity cost of implementing an intervention was close to zero, for example, the £8.20 self-administered acupressure band with instruction sheet (Molassiotis, Russell et al. 2013) or the £1.79 cost of adding magnesium to an asthma nebuliser (Powell, Kolamunnage-Dona et al. 2013). Interventions with vanishingly small opportunity costs may not require a full economic evaluation because there is no decision problem. Low cost internet or mobile phone based interventions may well fall under this category since implementation costs post development are often close to zero.

Finally, collecting and analysing irrelevant resource use and cost data does not represent good value for money. It is inefficient. It is a tedious and unrewarding task usually allocated to junior members of staff (but sadly not always!). A focus on relevant resource use would make better use of the time of research assessors and research health economists and make them more available to support a larger number of evaluations. Cost-effectiveness analysis reports would be more digestible and intelligible to clinical and lay readers and ultimately to decision makers. Results would be less prone to bias due to error, missing data and misinterpretation. There is a risk that important cost differences will be missed accidently or deliberately. However, this risk may not be worth the cost associated with including data that has no direct relevance to the fundamental economic question of whether the difference in outcomes between two interventions is worth the difference in costs.

Limitations

It is easy with hindsight to criticise the comprehensive inclusion of resource use in past economic evaluations. Economic evaluations in new treatment populations may not have any reliable information on whether successful treatments have broader effects on non-program resources as a result of a limited evidence base. Furthermore, many the studies in this sample of HTA reports were found to be cost-ineffective, thus no effect on non-program costs would be expected. However, future economic evaluations, based on the evidence presented here, would benefit from a more refined definition of relevant costs. Arguably, these definitions could have been refined using existing evidence, clinical opinion and an approach based on economic principles.

Conclusion and recommendations

The relevance of resource use collected in an RCT should be determined by the fundamental economic research question of whether the difference in costs is worth the difference in outcomes between competing alternatives. From an economic perspective the inclusion of irrelevant costs will be wasteful of research effort, and due to the nature of cost data, will confound results. Thus, more focus is needed on the resources required to deliver a new intervention compared to usual care. A trial-based economic evaluation should clearly describe the specific resources needed to deliver a new intervention, including directly attributable consequences such as the management of side

effects, and also the resources used to deliver alternative interventions or existing care. Program-related resource use and costs should always be reported separately. The default position should be that the inclusion of non-program resource use must be justified *a priori* based on economic principles of opportunity cost and marginal analysis. If non-program costs are to be included then baseline data will be needed to adjust for inevitable baseline differences. It is a fallacy that that trial randomisation can account for differences in irrelevant cost data, since the statistical power in RCTs is rarely adequate for economic evaluation. Wherever possible, resource use and costs should be reported in a disaggregated fashion with appropriate measures of dispersion, so that readers can identify specific sources of variability. Resource use identification based on the economic relevance of resource use items is more consistent with the theoretical framework underpinning economic evaluation and should produce more valid and informative assessments of cost effectiveness.

Table 1 Summary of mean program and non-program costs

Study Intervention (n)	Results	Program costs	Non-program costs	Author account for non-program cost difference
Stallard et al., (Stallard, Phillips et al. 2013) Classroom CBT for adolescent depression (n=1,064)	Not cost effective	CBT: £41.96 Attention control:£34.45 Control: £0 Difference (CBT:Control): £41.96	CBT: £484 Attention Control:£483 Control: £385 Difference (CBT:Control): £99	No comment
Forster et al., (Forster, Dickerson et al. 2013) Training programme for caregivers of inpatients after stroke (n=928)	Not cost effective	Intervention: £39 Control: £0 Difference: £39	Intervention: £54,820 Control: £55,636 Difference: - £816	Difference was not statistically significant
Powell et al., (Powell, Kolamunnage-Dona et al. 2013) Nebulised magnesium sulphate in acute severe asthma in children (n=508)	Cost effective	Intervention: £1.79 Placebo: £1.42 Difference £0.37	Intervention: £1,156* Placebo: £1,202* Difference -£45*	Difference was not statistically significant
Russell et al., (Russell, Edwards et al. 2013) Endosonography for cancer of oesophagus or gastricus (n=231)	Cost effective	Intervention: £551 Control: £0 Difference £551	Intervention: £21,218 Control: £25,021 Difference: -£3,803	Inpatient stays
Gates et al., (Gates, Perkins et al. 2013) Medication for acute respiratory distress syndrome (n=326)	Not cost effective	Intervention £26,966 Placebo £24,570 Difference £2,396	Intervention £7,724 Placebo £5,749 Difference £1,975	No comment

Salisbury et al., (Salisbury, Foster et al. 2013) Telephone assessment for physiotherapy (n=2,249)	Cost effective	Intervention £87 Control £79 Difference £8	Intervention £353* Control £378* Difference -£25	Outliers
Lenney et al., (Lenney, McKay et al. 2013) Medication for asthma control in children (n=63)	Inconclusive	Drug 1 £278 Drug 2 £306 Control £81 Difference (Drug1: Drug 2) -£28	Drug 1 £70 Drug 2 £37 Control £24 Difference (Drug1: Drug 2) £33	No comment
Banerjee et al (Banerjee, Hellier et al. 2013) Antidepressants for depression in dementia (n=326)	Drug 1 was cost effective if informal care cost included	Drug 1 £37 Drug 2 £7 Placebo £0 Difference (Drug1: Drug 2) £30	Drug 1 £4317 Drug 2 £6188 Placebo £5497 Difference (Drug1: Drug 2) -£1,871	Informal care
Underwood et al (Underwood, Lamb et al. 2013) exercise for depression in care home residents (n=798)	Not cost effective	Intervention £322 Control £5 Difference £317	Intervention £4,639 Control £4,251 Difference £388	Difference was not statistically significant
Grant et al (Grant, Boachie et al. 2013) Laparoscopic surgery for reflux (n=357)	Cost effective	Intervention £2,552 Control £1,282 Difference £1,270	Program costs only	Not applicable
Watson et al., (Watson, Crosby et al. 2013) stepped care for older drinkers (n=529)	Cost effective – dominant	Intervention £46 Control £2 Difference £44	Intervention £849 Control £1087 Difference -£238	Difference was not statistically significant
Molassiotis et al self-acupressure for chemotherapy related nausea(Molassiotis, Russell et al. 2013) (n=450)	Inconclusive	Intervention £8.20 Standard care £0 Sham intervention £8.20 Difference (Intervention:Standard care)£8.20	Intervention £211.80* Standard care £578* Sham intervention £244.80* Difference (Intervention:Standard care) -£366.20	Outliers
Lamb et al(Lamb, Williams et al. 2012) Stepped care in neck injuries (n=3,851)	Not cost effective	Not reported	Intervention £440 Control £336 Difference £104	Not applicable
Woods et al(Woods, Bruce et al. 2012) Reminiscence groups in dementia (n=336)	Limited evidence for cost effectiveness	Intervention £498 Control £0 Difference £498	Intervention £5,355 Control £4,309 Difference £1,046	Outliers
Pickard et al(Pickard, Lam et al. 2012) Three urethral Catheters	One was possibly cost-effective	Catheter1 £2153 Catheter2 £2097 Catheter3 £2144	Program costs only	Not applicable

(n=6,394)				
Bowen et al(Bowen, Hesketh et al. 2012) Communication therapy post stroke (n=170)	Not cost effective	Intervention £776 Control £295 Difference £481	Intervention £10,244 Control £13,257 Difference -£3,013 Adjusted -£371	Difference was not statistically significant
Sharples et al(Sharples, Jackson et al. 2012) Lung cancer surgery (n=241)	Intervention slightly less costly and more effective	Intervention £10,402 Control £11,154 Difference -£752	Program costs only	Not applicable
Chalder et al(Chalder, Wiles et al. 2012) Physical activity for depression (n=361)	Not cost effective	Intervention £252 Control £0 Difference £252	Intervention £3,336* Control £1,774* Difference £1562	Productivity losses
Brown et al(Brown, Powell et al. 2012) Surgical repair of aortic aneurisms (n=1,656)	Not cost effective	Intervention £15690 Control £5094 Difference £10,596	Program costs only	Not applicable
Crawford et al(Crawford, Killaspy et al. 2012) Group art therapy in schizophrenia (n=417)	Not cost effective	Art Therapy £641 Control £0 Difference £641 Art Therapy £641 Activity grp £445 Difference £196	Art Therapy £35,597 Control £37,447 Difference -£1,850 Art Therapy £35,597 Activity grp £43,350 Difference -£7,753	Difference was not statistically significant

* Including productivity losses

Table 2 Summary of missing data

Study Intervention (n)	Follow up	Missing cost data	Missing QALY data	Missing clinical data
Stallard et al., (Stallard, Phillips et al. 2013) Classroom CBT for adolescent depression (n=1,064)	12 months	Not reported	Not reported	20%
Forster et al., (Forster, Dickerson et al. 2013) Training programme for caregivers of inpatients after stroke (n=928)	12 months	33%	36%	31%
Powell et al., (Powell, Kolamunnage-Dona et al. 2013) Nebulised magnesium sulphate in acute severe asthma in children (n=508)	1 month	55%	55%	7%

Russell et al., (Russell, Edwards et al. 2013) Endosonography for cancer of oesophagus or gastricus (n=231)	12 months	47%	47%	8%
Gates et al., (Gates, Perkins et al. 2013) Medication for acute respiratory distress syndrome (n=326)	6 months	64%*	63%*	1%
Salisbury et al., (Salisbury, Foster et al. 2013) Telephone assessment for physiotherapy (n=2,249)	6 months	43%	43%	15%
Lenney et al., (Lenney, McKay et al. 2013) Medication for asthma control in children (n=63)	48 weeks	40%	40%	14%
Banerjee et al (Banerjee, Hellier et al. 2013) Antidepressants for depression in dementia (n=326)	39 weeks	30%	30%	30%
Underwood et al (Underwood, Lamb et al. 2013) exercise for depression in care home residents (n=798)	12 months	Not reported	Not reported	19%*
Grant et al (Grant, Boachie et al. 2013) Laparoscopic surgery for reflux (n=357)	5 years	52%	52%	42%
Watson et al., (Watson, Crosby et al. 2013) stepped care for older drinkers (n=529)	12 months	20%	20%	12.5%
Molassiotis et al self-acupressure for chemotherapy related nausea(Molassiotis, Russell et al. 2013) (n=450)	28 weeks	57%	70%	47%
Lamb et al(Lamb, Williams et al. 2012) Stepped care in neck injuries (n=3,851)	12 months	30%	30%	30%
Woods et al(Woods, Bruce et al. 2012)	10 months	31%	Not reported	28%

Reminiscence groups in dementia (n=488)				
Pickard et al(Pickard, Lam et al. 2012) Three urethral Catheters (n=6,394)	6 weeks	Not reported	Not reported	16%
Bowen et al(Bowen, Hesketh et al. 2012) Communication therapy post stroke (n=170)	6 months	40.5%	17.5%	10%
Sharples et al(Sharples, Jackson et al. 2012) Lung cancer surgery (n=241)	6 months	28%	14%	0%
Chalder et al(Chalder, Wiles et al. 2012) Physical activity for depression (n=361)	12 months	57%	46%	29%
Brown et al(Brown, Powell et al. 2012) Surgical repair of aortic aneurisms (n=1,656)	8 years	Not reported	Not reported	Not reported
Crawford et al(Crawford, Killaspy et al. 2012) Group art therapy in schizophrenia (n=417)	24 months	30%	24%	15%

* Based on survivors

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