

1 Cost-benefit of outcome adjudication in nine randomised stroke trials

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33 **Abstract:**

34 **Background:** Central adjudication of outcomes is common for randomised trials and should control  
35 for differential misclassification. However, few studies have estimated the cost of the adjudication  
36 process.

37 **Methods:** We estimated the cost of adjudicating the primary outcome in nine randomised stroke trials  
38 (25,436 participants). The costs included adjudicators' time, direct payments to adjudicators, and co-  
39 ordinating centre costs (e.g. uploading cranial scans and general set-up costs). The number of events  
40 corrected after adjudication was our measure of benefit. We calculated cost per corrected event for  
41 each trial and in total.

42 **Results:** The primary outcome in all nine trials was either stroke or a composite that included stroke.  
43 In total, the adjudication process associated with this primary outcome cost in excess of £100,000 for  
44 a third of the trials (3/9). Mean cost per event corrected by adjudication was £2295.10 (standard  
45 deviation: £1482.42).

46 **Conclusions:** Central adjudication is a time-consuming and potentially costly process. These costs  
47 need to be considered when designing a trial and should be evaluated alongside the potential benefits  
48 adjudication brings to determine whether they outweigh this expense.

49 **Keywords:** Adjudication, stroke, clinical trial

## 50 Introduction:

51 In randomised stroke trials, central adjudication of outcomes is common<sup>[1]</sup>. Adjudicators are typically  
52 blinded independent experts who review individual participant data and provide an assessment of  
53 outcome(s). Clinicians at local sites often assess the same outcomes but these data are commonly  
54 discarded. Central adjudication should reduce both random and systematic bias, but studies have  
55 shown that it has limited impact on the estimated treatment effect in randomised trials<sup>[1-3]</sup>. Thus, it is  
56 important to estimate the cost of the adjudication process, in order to establish whether the cost  
57 outweighs the perceived benefit of the process.

58 The cost of adjudication could be estimated as the direct cost paid to the adjudicator, which is often a  
59 menial amount (£10-15 per adjudication). However, this does not take into account the time it takes  
60 the adjudicator to undertake their assessment of the individual participant data. Furthermore,  
61 preparing data for the adjudicators, blinding and obtaining source information and general set-up  
62 costs are other expenses associated with the adjudication process that are borne by the co-ordinating  
63 centre (often a clinical trials unit). Thus, the cost of the adjudication process can be made up from (1)  
64 direct costs paid to the adjudicators; (2) time costs of the adjudicators; and (3) co-ordinating centre  
65 costs.

66 The aim of this study was to estimate the cost of central adjudication in randomised stroke trials and  
67 present this cost in terms of the number of events corrected by the central adjudication process.

68

## 69 Methods:

### 70 Data Collection

71 Authors of stroke trials included in a systematic review<sup>[1]</sup> were invited to provide data on the cost of  
72 outcome adjudication in an online questionnaire (see Supplemental Material, Cost of Adjudication  
73 Questionnaire). Data collected included time required to adjudicate events, adjudicators' approximate  
74 salary in today's costs and how disagreements were handled.

### 75 Benefit of Adjudication

76 Our measure of benefit of the adjudication process was the number of events corrected after  
77 adjudication. This outcome provides an estimate of the agreement between the adjudicators and site  
78 investigators and quantifies the extent to which the adjudication process changes the trial outcome.  
79 However, this measure does not take into account whether the adjudication process impacts on the  
80 treatment effect estimate. We collected the number of events corrected after adjudication in our  
81 previous systematic review<sup>[1]</sup>.

## 82 **Cost of Adjudication**

83 All costs were taken from a societal perspective and were reported in various currencies (Australian  
84 dollars, Euros, Pounds Sterling and New Zealand Dollars). If costs were not entered as pounds  
85 sterling, then all other currencies were converted into pounds sterling on 16<sup>th</sup> May 2019.

86 We calculated adjudicator hourly salary assuming that adjudicators worked 1680 hours a year (40  
87 hours a week for 42 weeks of the year). Total time was determined using the amount of time it took  
88 for each adjudication, the number of events adjudicated and whether events were adjudicated  
89 multiple times. In addition to staff salary costs assumed to be borne by employers rather than study  
90 funders, we also assumed that adjudicators were directly paid £10 per event from study funds. This is  
91 not paid in all studies; however, it enables a comparison between studies and where paid, is typical of  
92 the amount in UK studies. Costs of resolving disagreements was based on staff time only.

93 For each study, we assumed a fixed set-up cost to create a website for data sharing (brain scans,  
94 video footage etc.) and for adjudicators to submit their final assessments. We estimated this to require  
95 40 hours of a database programmer (cost £650). We also assumed that each adjudicated event  
96 required four hours of administrative time at the co-ordinating centre (cost £40 per adjudicated event).

## 97 **Statistical Analysis**

98 Continuous variables were summarised with mean and standard deviation, or median and  
99 interquartile range. Categorical variables were described with frequency counts and percentages. The  
100 cost per event corrected was determined for each trial and for all trials.

101

## 102 **Results:**

103 Authors from nine trials, comprising 25,436 participants, completed the questionnaire and these nine  
104 trials are included in this study<sup>[4-12]</sup> (Table 1). All outcomes adjudicated were either stroke or a  
105 composite including stroke, with two trials including transient ischaemic attack as part of their  
106 outcome of stroke (See Supplementary Material, Supplementary Table I). In the majority of the trials  
107 (7/9, 77%) adjudicators reviewed only those events identified by the site investigators, but for two of  
108 the studies adjudicators assessed a larger number of events, by adjudicating either suspected events  
109 or all participants (See Supplementary Material, Supplementary Table I). The time taken per  
110 adjudication range from five minutes to two hours. However, the trial with the lowest time had three  
111 adjudicators assess each event (Table 2). All other trials assessed each event either once or twice.  
112 The trial with highest adjudicator salary cost was around twice that of the lowest.

113 Three of the trials (33%) had no disagreements (see Supplementary Material, Supplementary Table  
114 II). For trials that had disagreements between adjudicators, the cost and time associated with this was  
115 far less than that associated with the original adjudication (Table 3). Two studies had no events  
116 corrected after adjudication, although the total cost of the adjudication process for both of these was  
117 less than £4,000. Three trials had a total estimated cost of the adjudication process in excess of  
118 £100,000. On average, across the seven trials with corrected events, adjudication cost £2,295.10 per  
119 event corrected (standard deviation: £1482.42).

## 120 Discussion:

121 In this analysis of nine randomised trials we found that, on average, adjudication costs approximately  
122 £2,300 per corrected event, with the total cost of adjudication exceeding £100,000 for three trials. Our  
123 study assumed a fixed cost of £40 per adjudication for the co-ordinating centre, as it was not possible  
124 to collect accurate data retrospectively on a trial-by-trial basis. Another study estimated the co-  
125 ordinating centre cost for the adjudication process in a thromboprophylaxis trial, to be approximately  
126 £55 per adjudicated event<sup>[13]</sup> compared to our assumption of £40. Thus, we may have marginally  
127 underestimated the total cost of the adjudication process.

128 The nine trials included in this study all had binary primary outcomes, and when these were  
129 composites, they were constructed from binary components. There may be different types of  
130 outcomes that have greater or worse cost-benefit of adjudication than the outcomes described in this

131 study. For example, outcomes with greater objectivity, such as disabling stroke, may have less need  
132 for adjudication when compared to more subjective outcomes, such as functional status measured on  
133 the modified Rankin Scale or causality of adverse events<sup>[14]</sup>. In addition, the method of adjudication  
134 could have large cost-benefit implications. For studies where adjudicators only assess site-reported  
135 events, the cost will be lower than studies in which all participants are adjudicated. However, when  
136 adjudicators only assess site-reported events, the adjudicators cannot identify additional events that  
137 could have been missed by the site investigators, potentially limiting the benefit of adjudication.  
138 Furthermore, the blinding status of the site investigators has the potential to influence the benefit that  
139 can be gained from adjudication<sup>[15]</sup>, and this information should be used when designing a clinical trial  
140 to understand the potential costs and benefits adjudication can bring.

141 This study has a number of limitations. Firstly, the nine trials included span a 30-year time interval and  
142 cover a range of academic and industry funded trials, as well as including funding agencies that have  
143 varied sources of financial support (e.g. charities, government agencies). Therefore, the variability in  
144 these factors may have contributed to the disparity seen between the time taken for adjudication,  
145 which may have influenced the estimated cost of adjudication in this study. Secondly, this study relies  
146 on retrospectively collected cost data. Some of the trials included in this study performed their  
147 adjudications decades ago, so it is possible that this data is not as accurate as data collected  
148 prospectively. However, this is the first study that we are aware of that has attempted to estimate the  
149 entire cost of the adjudication process.

150 As eluded to above, further research is warranted that prospectively collects the costs of central  
151 adjudication in an ongoing trial. A previous study showed that adjudications can take months to  
152 complete<sup>[14]</sup>, and a prospective study could accurately measure the time taken for the multitude of  
153 processes that are involved in implementing adjudication in a clinical trial. Furthermore, combining  
154 cost data with the approach of Kahan and colleagues<sup>[16]</sup> could give further understanding to the cost-  
155 benefit of increasing the number of adjudicators or varying the method of adjudication.

156 To conclude, central adjudication has been shown to control for differential misclassification and is  
157 important for trials where blinding is inadequate or impossible<sup>[15]</sup>. However, it can be costly, and these  
158 costs need to be estimated when designing a trial to evaluate whether the benefits of central  
159 adjudication outweigh the potential expense.

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165 AR, CW, LJW provided the data for the study; PJG analysed the data; All authors interpreted the  
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217

Tables:

**Table 1:** Characteristics of included trials

	Included (n=9)
<b>Year of main trial publication</b>	
1990-2000	2 (22%)
2001-2005	1 (11%)
2006-2010	2 (22%)
2011-2015	2 (22%)
2016-2018	2 (22%)
<b>Study design</b>	
Parallel	8 (89%)
Factorial	1 (11%)
<b>Type of trial</b>	
Primary prevention	1 (11%)
Secondary prevention	6 (67%)
Acute stroke	2 (22%)
<b>Participants randomised</b>	
Mean (SD)	2826 (2744)
Median [25 <sup>th</sup> , 75 <sup>th</sup> centile]	2739 [449, 3096]
Min, Max	129, 8164
<b>No. of sites</b>	
Mean (SD)	86 (49)
Median [25 <sup>th</sup> , 75 <sup>th</sup> centile]	79 [50, 123]
Min, Max	17, 172
<b>Intervention</b>	
Drug	6 (67%)
Surgery/procedure	2 (22%)
Other	1 (11%)
<b>Comparator</b>	
Placebo	2 (22%)
Standard care	6 (67%)
Surgery/procedure	1 (11%)
<b>Primary outcome</b>	
Stroke	6 (67%)
Composite including stroke	3 (33%)
<b>Blinding status of site investigators</b>	
Blind to treatment allocation	4 (44%)
Not blind to treatment allocation	5 (56%)

**Table 2:** Time taken for adjudication and dealing with disagreements

<b>Trial name</b>	<b>Events adjudicated</b>	<b>Number of adjudications per event</b>	<b>Time per adjudication (minutes)</b>	<b>Total time for adjudication (hours)</b>	<b>Adjudicator hourly salary</b>	<b>Cost of adjudication*</b>
CABACS	34	Once	10	5.7	£67.62	£723.18
ESPRIT	440	Three	5	110	£62.40	£20064
FASTEST	24	Once	45	18	£70.16	£1502.88
HAEST	93	Once	15	23.25	£47.62	£2037.17
J-STARS	239	Once	30	119.5	£47.62	£8080.59
NASCET	436	Twice	120	1744	£47.62	£91769.28
PROGRESS	992	Once	15	248	£48.22	£21878.56
TARDIS	1656	Twice	10	552	£49.40	£60388.80
VITATOPS	1260	Once	20	420	£96.40	£53088

\*Calculated as: Cost of adjudication = (Total time for adjudication)\*(Adjudicator hourly salary) + [(Events adjudicated)\*Number of adjudication per event]\*(£10)]

**Table 3:** Cost of adjudication per corrected event by included trial

<b>Trial name</b>	<b>Coordinating centre cost*</b>	<b>Adjudication cost</b>	<b>Disagreement cost</b>	<b>Total cost</b>	<b>Number of events corrected after adjudication</b>	<b>Cost per corrected event</b>
CABACS	£2010	£723.18	£0	£2733.18	0	NA
ESPRIT	£18250	£20064	£114.40	£38428.40	51	£753.50
FASTEST	£1610	£1502.88	£631.44	£3744.32	0	NA
HAEST	£4370	£2037.17	£0	£6407.17	2	£3203.58
J-STARS	£10210	£8080.59	£2381	£20671.59	10	£2067.16
NASCET	£18090	£91769.28	£1285.74	£111145.02	27	£4116.48
PROGRESS	£40330	£21878.56	£0	£62208.56	98	£634.78
TARDIS	£66890	£60388.80	£8348.60	£135627.40	34	£3989.04
VITATOPS	£51050	£53088	£1253.20	£105391.20	81	£1301.13
<b>Mean (SD)<sup>†</sup></b>						£2295.10 (1482.42)
<b>Median<sup>†</sup></b>						£2067.16
<b>Min<sup>†</sup></b>						£634.78
<b>Max<sup>†</sup></b>						£4116.48

\*Coordinating centre cost includes £650 set-up cost and £40 cost per event

<sup>†</sup>Summary statistics do not include CABACS or FASTEST