Outcome Measures for Emergency Care after a Seizure (OMECS)

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Abstract

Background

The care of patients who have a seizure and are seen by the ambulance service is still relatively primal. Most of these patients have a self-terminating episode and would not be classed as a medical emergency. Despite this, they are still transported to the Emergency Department (ED) where appropriate care options are limited. This disparity has led our enquiry into whether an alternative care pathway can navigate patient care to the right place, first time. In this study, we used certain outcome measures to power a research study to answer the above question, whilst demonstrating practical cost-effectiveness if implemented.

Methods

We obtained anonymised routine data from the Yorkshire Ambulance Service (YAS) from Jan to Dec 2016. We estimated key parameters with uncertainty to inform the sample size calculation. A preliminary health economics model informed the reduction in conveyance rate and trade-off with an increase in recontact rate that is likely to yield resource savings. The sample size for a parallel group cluster randomised trial (CRT) with co-primary hypothesis tests (superiority on conveyance and non-inferiority on recontacting at 30 days) was calculated under a number of scenarios.

Results

A 15% conveyance reduction is worthwhile to detect and an increase to 20% in recontact rate from 3% is clinically tolerable for safety. Assuming a 74% control conveyance, 90% power for a two-sided test to preserve a 5% type 1 error, and an intracluster correlation coefficient (ICC) of 0.044, a total of 70 paramedics (35 per arm) are required with each encountering an average of 9 patients (first incident encounters). Thus 630 patients (315 per arm) would be required for a CRT. This sample size will have >90% power to address recontact non-inferiority objective even for a small non-

inferiority margin of 5.3% for an ICC of 0.044 or less. We found an annual per-patient cost benefit of £33.21 for an economic reference case. The amount of capital saved by having the intervention for 630 patients (including set up costs) was £14,983.87. A univariate sensitivity analyses found that conveyance became cost-ineffective when there was only a 12% reduction. We found recontact became cost-ineffective when 11% or more patients recontacted.

Conclusions

A sample size using outcome measures which have an element of risk (non-conveyance) and mitigating them with a safety element (recontact) can be calculated. However, the level at which a study is clustered should be carefully considered. Clustering at paramedic level requires a larger sample size due to the variance between individual paramedics. The economic model shows the fragility of the outcome measures on cost-effectiveness. Nevertheless, there were still a majority of scenarios that would result in cost-effectiveness. The economic model is available from: https://www.sheffield.ac.uk/scharr/sections/dts/ctru/omecs

Introduction

Suspected seizures are a common cause of emergency calls to ambulance services. In England, it is estimated that suspected seizures give rise to approximately 211,000 calls to ambulance services (3.3% of all emergency incidents), 60,000 seizure-related Emergency Department (ED) attendances, and 40,000 hospital admissions per year.[1] The majority of suspected seizures self-terminate within 90 seconds and are not medical emergencies.[2] Most people who have experienced self-terminating epileptic seizures will fully recover without medical treatment nevertheless, the majority are unnecessarily transported to hospital which is the main direct cost of poorly controlled epilepsy.[3] The qualitative literature shows that many paramedics lack confidence in assessing these patients, feel they have not received adequate training, do not have access to decision support tools and see transport to hospital as safer from a medico-legal viewpoint.[4]

Safely reducing unnecessary transport to hospital is an NHS England CQUIN indicator, an aspiration of ambulance services and it is supported by patients.[5] Despite this there are no evidence-based tools to support paramedics[1] to reduce unnecessary transport to hospital after a suspected seizure and to meet the NICE quality standard of review by a specialist within two weeks of a suspected seizure.[6] Our aim was to develop a robust design to assess the effectiveness of a pre-hospital intervention to 1) safely reduce unnecessary transport to hospital and 2) to refer patients who were not transported to hospital to an epilepsy specialist nurse (ESN).

After a seizure, patients are often drowsy, confused and have reduced consciousness. Obtaining consent to undertake research or to provide self-report outcome data in the pre-hospital context for these patients is not feasible. Furthermore, studies that rely on

researchers contacting patients after they have recovered from a seizure are likely to be undermined by self-reporting and recruitment biases. There is also a high risk that patients from the most vulnerable and deprived sections of the population would be underrepresented. The use of routine data in pre-hospital research, especially linked data from multiple care providers (111, 999, A&E, in-patient HES data, ONS), is potentially a very powerful tool. We undertook preliminary work to inform the design and conduct of the definitive study, specifically to assess:

1) The suitability of the proposed outcome measures and their timing from a statistical and clinical perspective;
2) The study design and the nature of the hypothesis tests including estimation of nuisance parameters within the design;
3) The feasibility of an economic model incorporating outcome measures and study design; and,
4) The cost-effectiveness of running the trial including an assessment on the fragility of outcome measures and their effect on cost-effectiveness.

Methods

Statistical methods

We used the Advanced Medical Priority Dispatch System (AMPDS) – which codes the symptom and severity of each emergency call - for case selection. We obtained anonymised routine data from the Yorkshire Ambulance Services (YAS), from 1 January to 31 December 2016, for all incidents with an AMPDS Code 12: "Convulsions/Fittings".[7]

Data were summarised to estimate parameters of interest such as conveyance and recontact rates. The Wilson score method was used to compute confidence intervals (CIs) around proportions[8], and Bootstrap method to compute the CI around the median[9]. The intra-cluster correlation coefficient (ICC) with uncertainty were obtained via post-estimation using analysis of variance and mixed logistic regression model accounting for clustering with an unstructured covariance for sensitivity analysis. We used funnel plots to explore a variation on how paramedics convey patients.[10]

We estimated the sample size for a cluster randomised trial (CRT) under several scenarios of the estimated parameters.[11] The reduction in conveyance rates of interest used to estimate the sample size was informed by a preliminary the health economic model described below.

Health economic methods

The eligible population were male and female adult patients (≥ 18 years of age) who presented to the ambulance service following a suspected seizure and subsequently transported to the ED. There was no sub-group analysis. The study was designed to evaluate the costs versus benefits of not transporting people after a suspected seizure to the hospital. The perspective is a healthcare payer's perspective. The direct costs used national reference tariffs. The benefits were in terms of released funds to redistribute whilst simultaneously improving the care of people with epilepsy. Current practice was chosen as a control group. The intervention was ESN-referral on the scene.[1]

The primary outcome measure for this study was a reduction in the transportation of epilepsy patients to the ED. This is a short time frame as the benefit from an

intervention would be realised at the time of episode as opposed to in the future. The time horizon was set over one calendar year. No discount rate was applied.

Three preliminary studies were conducted and designed to answer 22 questions informing the model parameters. A cross-sectional study using routine data (n=132)[12] provided probability input data for epilepsy patients in both arms of the model and demographic information on presentation and transportation rates (questions 1-5). Another cross-sectional study (n=91)[13] provided probability outcome data for epilepsy patients in the ED for the control arm of the model and allowed complete mapping of the patient journey through the system (questions 6-8). A service evaluation into an alternative care pathway for epilepsy (n=87)[1] was populated the probability outcome data for epilepsy patients for the intervention arm of the model (questions 9-22). Ambulance resources were calculated from Yorkshire Ambulance reference tariffs 2016/17. General Practitioner (GP) and in-hospital consultant costs were based on NHS Health and Social Care reference costs.[14] Other costs were calculated from Department of Health reference costs.[15]

We developed a discrete-event simulation model with a time horizon of one year comparing usual care (control) with an Epilepsy Specialist Nurse (ESN) telephone referral on the scene (intervention). This model was chosen as patient events are short and do not tend to move through different health states. The primary assumption of the model is that the intervention would reduce the proportion of patients transported to the ED. Another assumption was the probability of death at any stage is zero because no published studies relevant to the model have evidenced death as an outcome. The threshold for cost-effectiveness was set at £0 as there was no per-patient cost-saving

threshold available by local or national standards. Set-up costs were calculated based on one middle-grade band 7 point 30 nurse salary according to NHS Agenda for Change as of 2017. The whole time equivalent (WTE) required was based on the sample size through the model multiplied by the median time required to process each patient in the sample[1].

The yearly cost of the intervention was calculated and compared to the cost of usual care. The model was set up with the ability to adjust three variables. The first was the percentage change in conveyance rate which was the primary outcome of the model. The base case set this at 15% which was the median of three different sample size scenarios created in conjunction with the economic model. The second was the number of patients in the model. This had an effect on the total cost of the intervention but not the incremental per-patient cost. The base case set this at 630 which was the sample calculated to detect a 15% reduction in ambulance conveyance. The third variable was the patient re-contact rate. The reference case set this at 3% in the control and 8.3% in the intervention which was derived from the sample size calculation. The method of analysis was initially descriptive with a univariate sensitivity analysis conducted on the percentage of conveyance and re-contact rates.

Results and conclusion

The choice of the clustering unit

The team discussed the feasibility of different clustering units with pre-hospital care researchers and a research paramedic. Options included clustering at paramedic, vehicle and station level. Due to paramedics working from different stations and on different

vehicles each shift, it left paramedics as the most feasible cluster unit which would lead to the least contamination.

Paramedics and clustering of patients

There were 2 459 paramedics (clusters). The median (95% CI) number of patients per paramedic crew per year was 5 (4.6 to 5.4) and an interquartile range (IQR) of 2 to 11, with a range of 1 to 61 patients. The conveyance rate ICC (95% CI) estimates were 0.044 (0.034 to 0.053) and 0.058 (0.046 to 0.074) based on analysis of variance and mixed logistic regression model with unstructured covariance models. Recontact rate ICC was very small (less than 0.0075).

Conveyance rate

From 1 January to 31 December 2016, 20 073 patients reported at least one seizure-related incident. Of these, 18 305 (91.2%) experienced a single seizure incident. The crude conveyance rate (transportation to ED) was 74.2% (95% CI: 73.6 to 74.8). The conveyance rate accounted for clustering by paramedic; 74.0% (95% CI: 73.2 to 74.7%). There seems to be considerable variation in the way paramedic convey suspected seizure patients around the 74.2% average as illustrated in Figure 1.

Figure 1. Variation in paramedic conveyance rates

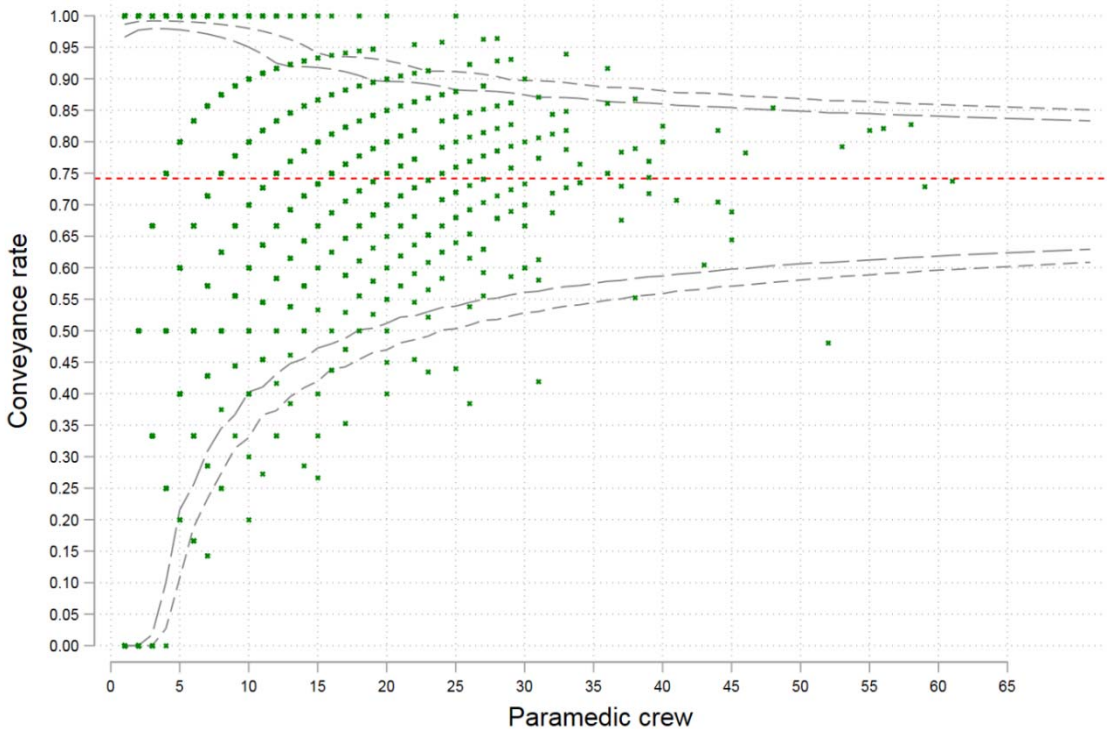


Figure note: control limits are set at 5% and 2% significance level.

Recontact rates

The overall recontact rate after the first event was only 1768 (8.8%). Table 1 summarises the cumulative distribution of time to recontact after the first incident within a certain number of days. For instance, only 0.5% (106/20073) recontacted within a day. Recontact rate within 7 days was only 269 (1.3%). In summary, recontact after the first event was rare and only 622 (3.1%) happened before 30 days of the first event. As a result, recontact rate on its own is unlikely to be a meaningful and feasible primary outcome to power the definitive study on. However, it was viewed as an important clinical marker for safety.

Table 1. Cumulative distribution of time to recontact (N=20 073)

Time to recontact after the first event	Cumulative n (%)
≤ 1 day	106 (0.5%)
≤ 2 days	143 (0.7%)
≤ 3 days	172 (0.9%)
≤ 4 days	190 (0.9%)
≤ 5 days	221 (1.1%)
≤ 6 days	244 (1.2%)
≤ 7 days	269 (1.3%)
≤ 14 days	394 (2.0%)
≤ 21 days	491 (2.4%)
≤ 28 days	603 (3.0%)
≤ 35 days	666 (3.3%)
≤ 42 days	756 (3.8%)

Sample size calculation

We estimated the sample size for a cluster randomised trial (CRT) under a number of scenarios with conveyance as the primary outcome assuming:

- 74% standard practice conveyance rate and ICC of 0.044;
- a 90% power for a two-sided superiority hypothesis test at 5% significance level;
- reduction in the conveyance of 10%, 15% and 20% likely to be cost-effective based on a preliminary health economics model described above;
- a 1:1 randomisation for a parallel group trial;
- a fixed number of paramedic (clusters) based on feasibility ranging from 50 to 120 with an increment of 10; and,
- a recruitment rate of 4, 5, or 6 patients per paramedic per month which around the median estimate.

Table 2 summarises the estimated sample sizes under these scenarios.

Table 2. Estimates of the sample size and recruitment duration under a number of scenarios

Standard care conveyance rate	Conveyance reduction	Total sample size for an iRCT	Fixed total number of paramedics	Average number of patients per paramedic accounted for ICC	Adjusted total sample size for a CRT	Estimated recruitment period (months) assuming a paramedic will encounter 4, 5, or 6 patients per year		
						4 patients	5 patients	6 patients
74%	10%	936	50	115	5750	345	276	230
			60	51	3060	153	122.4	102
			70	33	2310	99	79.2	66
			80	24	1920	72	57.6	48
			90	19	1710	57	45.6	38
			100	16	1600	48	38.4	32
			110	14	1540	42	33.6	28
			120	12	1440	36	28.8	24
	15%	440	50	15	750	45	36	30
			60	11	660	33	26.4	22
			70	9	630	27	21.6	18
			80	8	640	24	19.2	16
			90	7	630	21	16.8	14
			100	6	600	18	14.4	12
			110	5	550	15	12	10
			120	5	600	15	12	10
	20%	258	50	7	350	21	16.8	14
			60	6	360	18	14.4	12
			70	5	350	15	12	10
			80	4	320	12	9.6	8
			90	4	360	12	9.6	8
			100	3	300	9	7.2	6
			110	3	330	9	7.2	6
			120	3	360	9	7.2	6

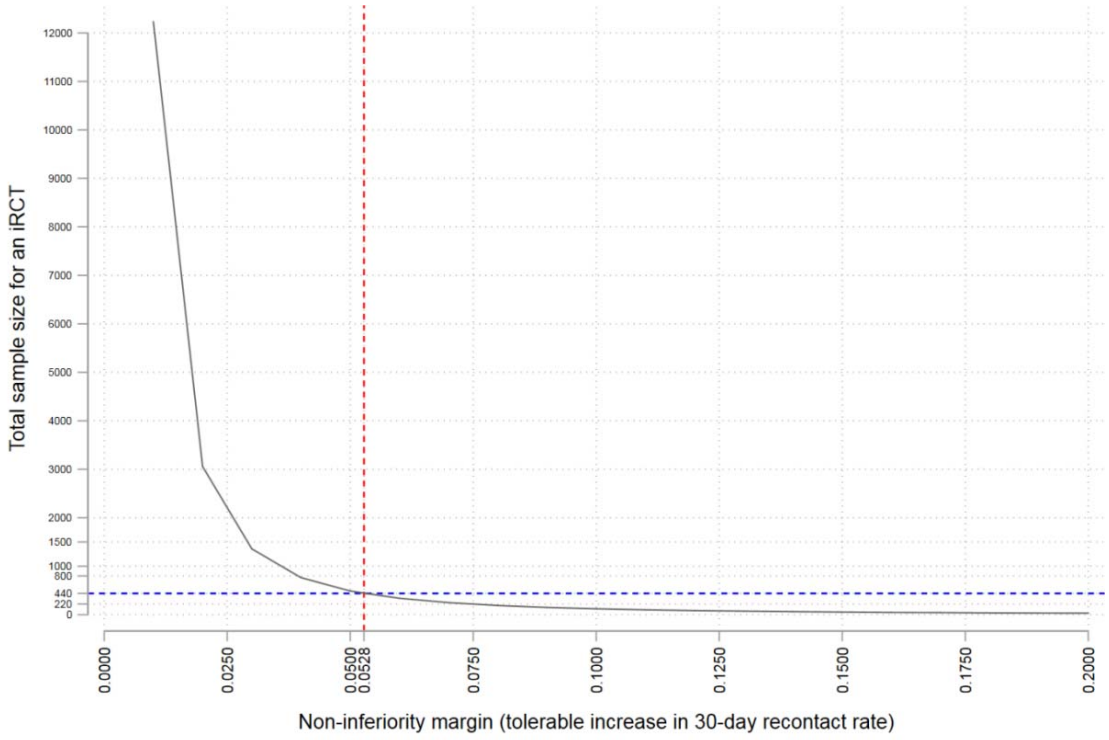
iRCT, individually randomised controlled trial, CRT, cluster randomised trial, ICC, intracluster correlation coefficient

We selected the highlighted desirable scenario based on feasibility of the trial within the proposed programme grant. A 15% absolute difference (AD) in conveyance rates was viewed worthwhile to translate to a meaningful reduction in health resources usage to declare superiority. This is equivalent to a risk ratio (RR) of 0.80 in favour of the intervention. With a control conveyance of 74%, an individually randomised clinical trial (iRCT) using 1:1 ratio would require a total sample size of 440 patients (220 per arm) to preserve a power of 90% for a two-sided test at 5% significance level. With 70 fixed total clusters (35 paramedics per arm) and an intra-cluster correlation coefficient (ICC) of 0.044, a paramedic will need to encounter an average of 9 patients (first incidences only) [11]. Thus, after adjusting for potential clustering by a paramedic, a total sample size of 630 patients (315 per arm) would be required for a CRT to fit in with our proposed study.

We resolved to include recontact rate within 30 days of the first incident (yes or no) as a co-primary endpoint to evaluate safety. The current practice recontact rate was around 3% and an increase of 20% attributed to the intervention was viewed clinically tolerable. It was also viewed that the intervention will need to be superior (on conveyance) and non-inferior (on recontact) to the current practice for it to be clinically acceptable in practice. When choosing two hypotheses in order to confirm superiority and non-inferiority there is no need to adjust for multiple testing.[16,17] Figure 2 shows how the recontact rate non-inferiority margin (NIM) for a given total sample size for an iRCT assuming a 3% usual care recontact rate to preserve a power of 90% for a one-sided test at 2.5% significance level. That is, based on the total 440 sample size using conveyance will have a 90% power to rule out a smaller non-inferiority margin of

5.28% increase in recontact rate (from 3% to 8.28%). This the study will also have more than 90% power for a 20% NIM (from 3% to 18%) to address this non-inferiority objective for an ICC of 0.044 or less.

Figure 2. Relationship between total sample size for an iRCT and re-contact non-inferiority margin



Feasibility of an adaptive design

A sample size re-estimation will be factored into the CRT design to validate the estimated number of first patient encounters per paramedic per year. This will be conducted after 12 months when most paramedics are expected to have encountered 50% of the expected patients. At this point, an optional futility analysis using stochastic curtailment will be considered.[18,19] The conditional power will be

calculated under a number of scenarios to aid decision-making by the independent data monitoring committee. For instance, assuming a 10-20% conveyance rate of the unobserved data including the estimate observed at interim. The trial could be stopped early for futility if the conditional power is less than 20%. The preliminary health economics model will also be used to aid decision-making given the estimates of conveyance reduction and recontact. This approach will help to incorporate the cost-effectiveness and safety into the decision-making process.

Preliminary health economic model

The base case simulation set at detecting a 15% reduction in ambulance transport for 630 patients with a 5.3% increase in recontact rate compared to the control (including setting up costs) gave an annual cost-benefit of £13.94 per patient. The amount of capital saved by having the intervention for 630 patients was £14,983.87, which theoretically could be redistributed to help other patients.

For the univariate sensitivity analysis of change in conveyance rate, the control and intervention recontact rate was held constant at 3% and 20% respectively. The sample size remained at 630. The incremental cost per one percentage point change was £6.75 per patient. This meant the intervention became cost-ineffective at a 12% reduction in conveyance (-£6.30). This is the inflection point when the intervention drops below the cost-neutral curve.

For the univariate sensitivity analysis of change in recontact rate, change in conveyance was held constant at 15%, the control recontact rate remained at 3% the sample of patients stayed at 630. The incremental cost per one percentage point change was £6.02

per patient. This meant the intervention became cost-ineffective when 11% of patients re-contacted (-£2.31).

In an extreme case analysis, when intervention recontact was set to 3% to match the control, it reduced the cost-effective threshold of change in conveyance rate down to 8% (compared to 11%). This means if the same quantity of patients recontacted the ambulance service following the intervention, and the intervention realised an 8% reduction in ambulance conveyance, commissioners would see a £0.93 cost saving per patient. When a change in conveyance was increased to 20%, it increased the cost-effective threshold of recontact to 16%. This means if the intervention realised a 20% reduction in the conveyance, commissioners would still see a £3.73 per patient cost saving, even with 16% recontacting following referral.

Conclusion

We found the data sources were feasible and showed success in the identification of epileptic patients. The outcome measure of reduction in conveyance was suitable and performed well. Re-contact is not suitable as a co-primary outcome measure due to limited recontact, however it is suitable to monitor patient safety during a trial.

The study design appears to be feasible and suitable with a single ambulance trust being able to generate enough events. Even when nuisance parameters are taken into account, the sample size and recruitment could occur within a programme grant timeframe.

The outcome measures could be transposed into an economic model using the outcomes of the sample size analysis. Furthermore, the outcome measures could be turned into variables for a sensitivity analysis.

The economic model demonstrated cost-effectiveness but this is relatively small within trial parameters. From a pragmatic view, the intervention is designed to improve patient care and comes at a cost-benefit to commissioners compared to usual care. The outcome measures are quite fragile in that they will only tolerate small percentage adjustments before becoming cost ineffective. Overall there were still more scenarios in the sensitivity analysis that were cost effective.

Dissemination

This work will be published in a peer reviewed journal. It will be submitted for publication at the UKCRC CTU Network director's group, the Emergency Medicine clinical studies group annual meeting and the ENS999 Forum annual meeting.

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Munya Dimairo (Statistician, CTRU), Jamie Miles (Research Paramedic, Yorkshire Ambulance Service and Research Assistant, ScHARR), Jon Dickson (Senior Clinical Lecturer, Academic Unit of Primary Medical Care) and Daniel Hind (Assistant Director, CTRU), together drafted this report.

The following conceived of or designed the work: Munya Dimairo, Jamie Miles, Jon Dickson, Daniel Hind, together with Suzanne Mason (Professor of Emergency

Medicine), Janette Turner (Reader in Emergency & Urgent Care Research), Markus Reuber (Professor of Clinical Neurology) and Tracey Young (Senior Research Fellow).

The following were involved in the acquisition of data for the work: Munya Dimairo, Jamie Miles, Jon Dickson, together with Trevor Baldwin (Assistant Director, Access & Response, Yorkshire Ambulance Service).

The following were involved in the analysis of data: Munya Dimairo, Jamie Miles, Tracey Young.

Munya Dimairo, Jamie Miles, Tracey Young and Jon Dickson were involved in the interpretation of data for the work.

All authors were involved in the final approval of the version to be published.

All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing interests

All authors declare that they have no competing interests.

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