Using the Barthel Index and modified Rankin Scale as outcome measures for stroke rehabilitation trials; a comparison of minimum sample size requirements

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Background

Underpowered trials risk inaccurate results. Recruitment to stroke rehabilitation randomised controlled trials (RCTs) is often a challenge. Statistical simulations offer an important opportunity to explore the adequacy of sample sizes in the context of specific outcome measures. We aimed to examine and compare the adequacy of stroke rehabilitation RCT sample sizes using the Barthel Index (BI) or modified Rankin Scale (mRS) as primary outcomes.

Methods

We conducted computer simulations using typical experimental event rates (EER) and control event rates (CER) based on individual participant data (IPD) from stroke rehabilitation RCTs. Event rates are the proportion of participants who experienced clinically relevant improvements in the RCT experimental and control groups. We examined minimum sample size requirements and estimated the number of participants required to achieve a number needed to treat within clinically acceptable boundaries for the BI and mRS.

Results

We secured 2,350 IPD (18 RCTs). For a 90% chance of statistical accuracy on the BI a rehabilitation RCT would require 273 participants per randomised group. Accurate interpretation of effect sizes would require 1000s of participants per group. Simulations for the mRS were not possible as a clinically relevant improvement was not detected when using this outcome measure.

Conclusions

Stroke rehabilitation RCTs with large sample sizes are required for accurate interpretation of effect sizes based on the BI. The mRS lacked sensitivity to detect change and thus may be unsuitable as a primary outcome in stroke rehabilitation trials.

Research waste is estimated to cost £132 billion each year (1) and recruitment difficulties contribute to this waste (2). When recruitment targets are met, trials are more likely to accurately identify significant result (3-6), interpret treatment effect sizes (7-10), and avoid research waste (1, 11-13). However, randomised controlled trials (RCTs) may fail to reach recruitment targets, take longer to recruit than originally forecast, require time or monetary extensions, or end early (3, 5, 14-18). Fewer than one third of RCTs funded by the UK's Health Technology Assessment (HTA) or Medical Research Council (MRC) from 1994 to 2002 met recruitment targets and over half were awarded extensions (14). Recruitment to RCTs between 2002 and 2008 only modestly improved with just over half meeting recruitment targets (19). Recruitment of stroke survivors to RCTs can be particularly challenging (17, 18, 20). For large (>300 participants) pharmacological stroke RCTs conducted between 1990 and 2004 an average of 0.79 participants were recruited per site per month (17), decreasing to 0.41 in a more recent review (20).

Stroke rehabilitation RCTs typically screen large numbers of stroke survivors to achieve their target sample size and on average recruit one participant per site per month (21). The 512 stroke rehabilitation RCTs published between 2005 and 2015 had a median sample size of 34 (IQR 21.25 to 60) participants each. Only two RCTs recruited more than 500 participants (21). Fewer than one third reported a-priori sample size calculations, increasing the risk of misleading results and research waste through underpowered statistical analysis (21).

The traditional a-priori approach to sample size calculations can lead to RCTs with inadequate statistical power, reducing the chance of detecting treatment effects and increasing the risk that results do not capture the magnitude of the effect (8, 10, 22-24). Power calculations for RCTs are undertaken to ensure a significant result is obtainable at a given power value (typically set at $\alpha = 0.05$ and $1-\beta = 0,9$), thus lowering the probability of type I (α) and type II (β) errors (8). During trial development the ability to evaluate the effect size of a treatment is rarely a priority,

instead the focus is on the trial's confidence in statistically significant levels by controlling for type one and type two errors (8). Accurate sample size requirements, using a-priori calculations based on evidence of estimated effect sizes may be key to ensuring that sample size targets protect against unreliable results.

Aim

To examine and compare the adequacy of participant sample size estimates for RCTs of stroke rehabilitation interventions using the Barthel Index or modified Rankin Scale in relation to statistical accuracy and effect size interpretation.

Methods

Simulations

The Barthel Index (BI) (25) and the modified Rankin Scale (mRS) (26) are commonly used measures of stroke survivors' disability and independence (25, 27, 28) and have been reliably used for previous simulation-based studies (29, 30). The mRS was also recently recommended by the Stroke Recovery and Rehabilitation Roundtable as an outcome measure for functional disability in stroke rehabilitation trials (28).

Our computer simulations were conducted using typical experimental event rates (EER) and control event rates (CER) for the BI and mRS in order to determine appropriate sample size boundaries (8). The CER was the proportion of people who experienced a clinically relevant improvement within the control group. The EER was the proportion of people that experienced a clinically relevant improvement within the experiential group (8). For the BI this was classified as an improvement by 1.85 points (or 9.25 for BI when scored 0-100)(31) and for the mRS as an improvement of 1 point (32, 33).

To develop CERs and EERs, the BI and mRS were converted into dichotomous variables (22). Reliable methods of dichotomisation, converting continuous measures into binary outcomes for meta-analysis and simulation purposes, were followed (22-24). Number needed to treat (NNT) was selected as the marker of clinical usefulness (8, 29, 30, 34). The NNT boundary was plus or minus 1 in order to tailor the algorithms to stroke rehabilitation NNTs which are typically larger than the post-analgesic RCTs that were used to develop these simulations (8).

Our first set of simulations examined the probability of observing a statistically significant effect of the intervention with increasing group sizes. The second set of simulations aimed to determine clinical relevance through of the our chosen measure of clinical relevance, the NNT.. We calculated the sample sizes required for trialists to be confident that the results accurately estimate the significance level and effect size of an intervention using varying group sizes and experimental event rate ranges. The purpose of this approach was to discover the sample sizes required for certain defined probabilities (from 0.5 to 0.95) that the value of the number needed to treat was credible, within clinically acceptable bounds (i.e. +/- 1 of its true value). Our simulations indicate how many stroke survivors should be included within stroke rehabilitation RCTs that use the BI or mRS as an outcome measure, to be confident in statistical accuracy and effect size interpretation.

Data usage

Stroke rehabilitation RCTs were included if IPD was potentially available from each trial's experimental and control group. Our IPD inclusion criteria were: 1) stroke survivors who participated in stroke rehabilitation RCTs (individual or cluster), 2) BI or mRS data at baseline and six months post-randomisation, 3) diagnosed with stroke 4) aged at least 18 years, 5) no significant visual or hearing impairments, 6) no history of dementia, and 7) able to participate in the RCT assessment schedule. Control group interventions were classified as 'usual care'.

IPD exclusion criteria were: 1) significant levels of pre-morbid disability, 2) serious medical illness or instability, and 3) early deterioration.

The Virtual Stroke Trials Archive (VISTA) is a collaboratively formed database of anonymised IPD from completed stroke RCTs which provides access for secondary analysis to inform future RCT design. The VISTA-Rehab archive currently contains IPD data for 11,526 stroke survivors from 52 stroke rehabilitation RCTs. We extracted data for both the experimental and control conditions.

Three sets of data were used for the mathematical modelling:

- IPD for experimental and control groups (usual care or inactive control).
- Experimental and control event rates (calculated using the IPD).
- Typical group sizes commonly used for stroke rehabilitation RCTs (extracted from a previously conducted systematic review (21).

Our use of fully anonymised data from VISTA (35) for novel research purposes had institutional ethical approval (University of Glasgow, Medical Veterinary and life science ethics). Data was stored on a secure server by the Robertson Centre for Biostatistics, University of Glasgow, UK and accessed via a virtual private network.

Results

Of 11,526 possible IPD from 52 RCTs, 2,350 IPD from 18 RCTs were eligible for inclusion in our simulations (Figure 1). BI was available for 1,782 IPD (696 participants within a control group and 1,086 participants within an experimental group) and for the mRS 568 IPD were available (223 participants from a control group and 345 participants within an experimental group). Time between stroke onset and inclusion in the RCTs ranged from 24 hours to 5 years after stroke.

Insert Figure 1

Barthel Index simulation

The CER and the EER were calculated for the Barthel index:

- CER: in the control conditions 250 of 696 participants experienced improvement of at least 1.85 (2) on the BI. The CER was 0.36 (250 IPD improved divided by 696 total participants).
- EER: within the experimental conditions there were 466 of 1086 participants who experienced improvement of at least 1.85 on the BI. Therefore, the EER was 0.43 (466 IPD improved divided by 1,086 total participants).

Table 1 illustrates the group sizes required to accurately detect a statistically significant effect, with probabilities of 0.5 to 0.95 using the BI (with a significance level of 0.95, a CER of 0.36, and an EER from 0.4 to 0.9). The sample size projected for statistical tests becomes increasingly accurate for samples larger than 10 participants (8).

Insert Table 1 about here

For a 90% chance that the statistical significance level is correct (assuming a CER of 0.36 and EER of 0.50) 273 participants per group would be required (see column 4 of Table 1). For typical stroke rehabilitation group sizes to have a 90% probability that the statistical advantage of the intervention over the control condition is accurate would require an experimental event rate of around 0.70 (see column 6 of Table 1). Based on an EER 0.43 and CER 0.36 to have a 90% probability of observing a significant effect on the BI more than 1,000 participants would be required in each group (column 3 of Table 1).

Group sizes required for probability 0.5 to 0.95 of obtaining a clinically relevant NNT with the CER 0.36 and EER ranged from 0.40 to 0.80 for the BI are shown in Table 2.

Insert Table 2 about here

For effect size interpretation on the BI, sample sizes five times as large as those needed for significance level accuracy would be required (unless EER is above 0.70) (Table 2). For the commonly used group sizes of between 20 to 40 participants, only an intervention effect size of 0.80 would allow for exploration of how effective a treatment had been. For a CER of 0.36 and an EER of 0.43 more than 1,000 participants would be required in each group for accurate effect size interpretation.

Modified Rankin Scale simulation

We also calculated the true control event rate (CER) and the experimental event rate (EER) for the modified Rankin Scale IPD:

- CER: in the control conditions 30 of 223 participants experienced improvement of at least 1 on the mRS. Therefore, the CER was 0.13 (30 IPD improved divided by 223 total participants).
- EER: within the experimental conditions there were 43 of 345 participants who experienced the event. Therefore, the EER was 0.12 (43 IPD improved divided by 345 total participants).

The event rate for the control condition (the participants who experienced improvement of at least 1 point on the mRS) was higher than the experimental condition, thus simulations were not possible for the true CER and EER. However, we used a range of potential EER rates to reflect the sample sizes required for studies that may experience higher EER than the IPD used in this analysis (Table 3 & 4).

Our simulations of the group sizes required to obtain probabilities of 0.5 to 0.95 of having a statistically significant results at the level of 0.95, with a CER of 0.13 and an EER from 0.2 to

0.7 (Table 3). Again, the calculations for the smallest number of group sizes required are probably not accurate with less than ten participants.

Insert Table 3 about here

As the control group experienced more clinically relevant improvement than the experimental group, the event rates calculated on the available data would at no point provide an accurate interpretation of the statistical significance levels, regardless of how large the group size became. Hypothetical event rates to illustrate the potential group size requirements can be seen in Tables 3 and 4.

The group sizes required for probability 0.5 to 0.95 of obtaining a clinically relevant NNT with the CER 0.13 and EER ranged from 0.20 to 0.60 are presented in Table 4.

Insert Table 4 about here

Discussion

Substantially more participants would be required for both accurate assessment of statistical significance levels and for effect size interpretation in stroke rehabilitation RCTs using the BI as an outcome when compared to recent RCT sample size trends within this field (36). A large portion of individuals allocated to RCT control groups experienced positive improvement on the BI that was classified as clinically relevant. The BI may be oversensitive to positive change or data reflects spontaneous recovery following stroke, leading to an inflated CER and an increased sample size target. Stroke rehabilitation RCTs often compare the experimental intervention with 'usual care' which is known to be effective therefore the high CER could reflect genuine and meaningful change for stroke survivors.

The mRS lacked the sensitivity to reflect rehabilitation improvements in our data and it was not possible to estimate the required sample sizes for RCTs . The treatment effects within the control conditions were higher than those observed within the experimental conditions. This may suggest that the RCTs' experimental interventions were ineffective or produced a negative result or that the absence of effect reflects the mRS's lack of sensitivity to rehabilitation improvement. Similar simulations using acute stroke RCT data found that the sample sizes required to detect change on the mRS were typically unclassifiable because of the lack of treatment effect sensitivity (29, 30). This does not cast doubt on the utility of the mRS as a baseline measure (28, 37) but our findings raise important questions about the usefulness of the mRS as an outcome measure within the context of stroke rehabilitation RCTs.

Stroke rehabilitation RCTs should use carefully selected primary outcomes to capture treatment effects for stroke rehabilitation interventions. Our simulations have provided some indication of the minimum sample size requirements for trials that use the BI as an outcome measure. These minimum sample sizes for RCTs could contribute to improved treatment effect evaluations by reducing the reliance on underpowered RCTs (3-5, 38). Stroke rehabilitation RCT samples of an adequate size for the BI are possible (36) despite the significant costs associated with running large RCTs (39) and pooling pre-existing data across multiple datasets to conduct meta-analysis may facilitate effect size interpretation.

Strengths and limitations of the study

Our simulation methodology and algorithm were successfully applied to IPD from several international, multidisciplinary stroke rehabilitation RCTs (8). In contrast to simulations using hypothetical data (30), we generated the CER and EER from a representative stroke rehabilitation RCT IPD dataset. While availability of IPD was limited by our requirement for mRS or BI data at both baseline and a subsequent time point, our analysis represents the best possible current estimate. The BI has a known celling effect and therefore some participants

scoring at the ceiling point at baseline that were unable to reflect positive change on this scale (40). Recent research has suggested that the chronicity of stroke patients is important when interpreting the sensitivity of the BI. We were unable to control for time post-stroke in our simulations. The degree of variability observed in the CER and EER may have been caused by the differing stroke rehabilitation interventions and post-stroke recruitment windows.

Conclusions

The BI may be useful outcome in stroke rehabilitation RCTs with sufficient sample sizes to support accurate interpretation of statistical significance levels. The mRS lacked sensitivity to detect change and thus may be unsuitable as a primary outcome in stroke rehabilitation trials.

***VISTA-Rehab Steering Committee**

Brady M.C (Chair), Ali M, Ashburn A, Barer D, Barzel A, Bernhardt J, Bowen A, Drummond A, Edmans J, English C, Gladman J, Godecke E, Hiekkala S, Hoffman T, Kalra L, Kuys S, Langhorne P, Laska AC, Lees K, Logan P, Machner B, Mead G, Morris J, Pandyan A, Pollock A, Pomeroy V, Rodgers H, Sackley C, Shaw L, Stott DJ, Sunnerhagen KS, Tyson S, van Vliet P, Walker M and Whiteley W.

Declarations

Conflicting interests

The Author(s) declare(s) that there is no conflict of interest

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Availability of data and materials

The dataset used and analysed in this study is available from VISTA-Rehab.

Authors' contributions

KMcG, MCB, CS, JG were responsible for the design of the study. MA identified eligible IPD and cleaned the dataset for analysis. KMcG carried out all simulations using software provided by and guidance from DG. KMcG prepared the draft manuscript. MB, CS, JG, MA and DG provided critical revisions of the document. MCB, CS and JB secured the funding to support the study. All authors have approved the final manuscript.

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