Study design and analysis plan for a clinical trial to investigate Motivational Interviewing for improving outcome following stroke

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Background

Patients who experience stroke often encounter psychological problems after their experience. This has been found by research such as Bergersen et al. (2010), which concluded that almost half of their investigated patients with stroke had psychiatric problems. These problems are effecting the recovery of these patients. Factors responsible for this include depression, as patients lack motivation to rehabilitate, therefore making less progress and resulting in shorter survival. Current treatment is in the form of standard therapy and focuses on improving the mood of patients through problems solving. There is a lack of evidence supporting these methods, but it has been shown that patient's beliefs and expectations post stroke effect their recovery.

As a result, one type of problem solving known as motivational interviewing can be considered. Motivational interviewing "explores the client's own arguments for change. The interviewer seeks to evoke this "change talk"—expressions of the client's desire, ability, reasons, and need for change—and responds with reflective listening." Hettema et al. (2005). This has been found to be effective for increasing recovery in mental health problems. Thus, this technique may improve the mood of stroke patients, which may improve functional outcome. This trial aims to investigate whether motivational interviewing can improve stroke patients outcome compared to the standard therapy. However, the trial should also aim to investigate the practicality of this type of therapy compared to the standard.

Patient selection

Patient selection will be based upon the inclusion and exclusion criteria. This criteria has been chosen to strike a balance between the variability of study populations against reduced opportunities for generalisations as outlined by Meinert (1986). This means the criteria has been chosen so enough participants are included so the study findings can be generalised to the greater population whilst also making sure participants with specific factors enter the study. The inclusion criteria includes that the patient has experienced a stroke in the past year, the patient is at least 18 years of age and the patient is medically stable. Exclusion criteria includes an inability to provide informed consent, the patient has experienced recurrent strokes, the patient has already undergone therapy post stroke, the patient has been previously diagnosed with subarachnoid haemorrhage, the patient has another condition likely to impact participation in trial and the patient has impairments precluding participation. Ineligible patients will be excluded from the analysis.

Treatment schedule

Patients allocated to the treatment group will receive four one-hour motivational interview sessions over a period of six weeks, whereas control group patients will receive four one-hour standard therapy sessions for stroke patients over the same period. Evaluators will be trained in either motivational interviewing or standard therapy. Each patient will have the same evaluator throughout all of their sessions.

Patient Evaluation

The patients will be initially evaluated for inclusion in the trial, along with information about their history of depression, functional independence and age, for use of randomisation. The patients mood will be evaluated using the General Health questionnaire. This is a 28 question questionnaire with a score of 0-3 for each question, giving a total range of 0-84, high scores indicating high distress. It identifies minor psychiatric disorders which is suitable for all ages above adolescence. It assesses the respondent's current state and asks if that differs from his or her usual state. It is sensitive to short term disorders but not to long standing attributes of the respondent. Patients will be measured at baseline by taking the questionnaire, to give a value of their initial mood. This will occur at 7 days post stroke. Patients will then take a second GHQ-28 3 months after treatment via mail. The primary endpoint is the mean difference in score of the two questionnaires. A difference in score of 10 or more is clinically relevant.

Trial design

The trial will be a phase III blinded randomised controlled trial. The investigators assessing and analysing the results will be blinded to the patients assignment to treatment. It is not possible to blind the participants from the treatment, as they may be able to determine whether they receive the standard therapy or the motivational interviews. The essential data collection, measurement, reading and classification procedures on individual patients will be made by personnel who have no knowledge of the treatment assignment or course of treatment. As the actual evaluators, that being those conducting the motivational interviews and therapy, will know the assignment of treatment, one set of personnel will administer the treatments and another set will collect the data needed for assessment. The assistant carrying out the randomisation will also have no further participation in the study. Careful explanation of the schedule as well as the trial objectives is crucial for compliance, Pocock (1983), therefore there will be an informative pamphlet for all participants to read. Regular check-ups will also be required, as well as follow-up to ensure full evaluation of participants.

Randomisation

The patients are randomised to treatment to avoid bias due to differences in clinical and demographic characteristics and to support the independence assumption underlying many statistical procedures. Patients will be randomised to treatment via the minimisation method with weighted probability 0.75 with the following factors: history of depression (yes/no), degree of functional independence (good, moderate or poor) and age ($< 65, \geq 65$). Simple randomisation is used when the groups are balanced, but when they are unbalanced, the patient is allocated based on minimisation score to achieve balance. As the general method doesn't include any element of randomness, we have introduced the assignment to the smaller score with probability 0.75 which helps stop investigators from predicting patient assignment, (Pocock (1983)). This worsens the overall imbalance between groups, but improves balance for the chosen variables compared to simple randomisation. The advantages here includes balance between a number of factors when there are modest treatment effects.

Statistical analysis

As we are interested between the difference in the test scores, these will be calculated for each subject in both groups and a mean difference of each group will be calculated, an unpaired two sample t-test will then be used to analyse the data. This will show whether there is an actual statistically significant difference in mood change between the treatment and control group. This will test the following hypotheses:

$$H_0 : D = \mu_1 - \mu_2 = 0 \tag{0.1}$$

$$H_1 : D \neq 0 \tag{0.2}$$

The test statistic under H_0 and standard error are:

$$T = \frac{\bar{D} = \bar{\mu_1} - \bar{\mu_2} - 0}{SE(\bar{D})} \tag{0.3}$$

$$SE(\bar{D}) = S\sqrt{\frac{1}{n_1} + \frac{1}{n_2}} \tag{0.4}$$

$$S^2 = \frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2} \tag{0.5}$$

We will reject the null hypothesis if $|T| > t_{1-\alpha/2, n_1+n_2-2}$. Corresponding 95% confidence intervals will be calculated as:

$$\bar{D} \pm t_{n-2,1-\alpha/2} S\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}$$

From the results, we can infer from the test statistic whether D is significantly different from zero. Whereas the confidence interval will show the plausible range for the effective difference. However, statistical significance does not imply clinical relevance. This will be achieved if $D \geq 10$.

Required sample size

Recall the primary endpoint is the difference in scores. The analysis will be a two sample t-test and so the test statistic $t = \frac{\bar{D} = \bar{\mu_1} - \bar{\mu_2} - 0}{SE(\bar{D})}$. The null hypothesis assumes that there will be no difference in the mean score difference between the control and treatment groups, whereas the alternative hypothesis assumes there will be a difference.

Firstly, the sample size can be determined by deriving a formula for n. Under H_1, $\theta = \theta^*$, as the power $= P(|Z| \geq \Phi^{-1}(1-\alpha/2)|H_1 \text{ true}) = 1-\beta$, this implies $1-\Phi(\Phi^{-1}(1-\alpha/2)-\theta^*) \approx 1-\beta$ so by rearranging for θ^*:

$$\theta^* = \Phi^{-1}(1-\alpha/2) + \Phi^{-1}(1-\beta)$$

We have two groups, the control and treatment groups which data both follow a normal distribution, both groups have the same mean except, under H_1, the treatment group has a clinically relevant difference Δ^* so, $X_{1i} \sim N(\Delta^* + \mu, \sigma^2)$, $X_{2i} \sim N(\mu, \sigma^2)$. Therefore, as we have a parallel group design,

$$\bar{X}_1 - \bar{X}_2 \sim N(\Delta^*, \sigma^2(\frac{1}{n_1} + \frac{1}{n_2}))$$

Dividing by the standard deviation,

$$\frac{\bar{X}_1 - \bar{X}_2}{\sigma\sqrt{1/n_1 + 1/n_2}} = Z \sim N(\frac{\Delta^*}{\sigma\sqrt{1/n_1 + 1/n_2}}, 1)$$

By introducing r as the proportion of the sample that will be undergoing motivational interviewing, so $n_1 = rn, n_2 = (1-r)n$, the above equation becomes,

$$Z \sim N(\frac{\Delta^*}{\sigma\sqrt{1/rn + 1/(1-r)n}}, 1)$$

Rearranging the denominator,

$$Z \sim N(\frac{\Delta^*\sqrt{nr(1-r)}}{\sigma}, 1)$$

Therefore,

$$\theta^* = \frac{\Delta^*\sqrt{nr(1-r)}}{\sigma}$$

Now using the equation from earlier and replacing θ^*,

$$\frac{\Delta^*\sqrt{nr(1-r)}}{\sigma} = \Phi^{-1}(1-\alpha/2) + \Phi^{-1}(1-\beta)$$

And to find n, the equation can be rearranged,

$$n = \frac{\sigma^2}{r(1-r)\Delta^{*2}}(\Phi^{-1}(1-\alpha/2) + \Phi^{-1}(1-\beta))^2$$

As a result, to detect a clinically relevant difference of 10 with a two sided type 1 error rate of 5% and a power of 80%, were the standard deviation of the data is 18, a sample of size 104 is required. Therefore, 52 patients to each group. Sakpal (2010) states we should consider a dropout rate d and then calculate the sample size as $n_1 = n/(1-d)$. If we assume that we can expect a 10% dropout rate, a sample size of 116 (58 per group) would be appropriate to account for any dropout and still achieve the required sample size.

Intended handling of protocol deviations

Protocol deviations are classified as "any departure from the intended treatment and/or evaluation" by Pocock (1983). Deviation can occur in the form of non-compliance or patient withdrawal and incomplete evaluations. All protocol violations, deviations and missing values will be documented in the clinical study report and their potential influence on the study results will be described.

Non-compliance should be minimised due to measures in the trial design such as informative pamphlets. However, if non-compliance occurs, this should lead to prompt action by the staff to ensure compliance. If persistent non-compliance occurs, the patients involvement in the trial will not continue and this should be reported to the regulatory authorities. There inclusion in analysis will be treated the same as withdrawals below.

Patient withdrawal can arise due to patient refusal to participate or clinical judgement that the patient should be transferred to alternative therapy. To minimise refusal, and to adhere with the ethics of the trial, participants are able to withdraw from the study at any point. Participants who withdraw or are loss to follow up will be included in the analyses up to their last completed assessment, as per the intention to treat principle. This principle requires all randomised subjects be included in the primary analysis, which would require follow up of all randomised subjects. This is important for reducing bias and providing a secure basis for statistical tests. To then assess the robustness of results to the inclusion of data, sensitivity analysis in the form of per protocol analysis will be carried out. Sensitivity analysis is defined as "a method to determine the robustness of an assessment by examining the extent to which results are affected by changes in methods, models, values of unmeasured variables, or assumptions", (Dennis et al. (2013)). Consistency between the primary and sensitivity analysis is important as it will strengthen the conclusions and credibility of the findings.

Specialist planning issues

The trial should be aimed at having no external backing and being locally based, as Pocock (1983) states, this type of funding applies to non-drug therapy. As the trial will be locally based, the day-to-day coordinator will be a junior doctor, whilst the principal investigator will be a consultant. The trial may require a monitoring committee if funding can make this possible. Participants must be fully informed and able to carry out his responsibilities. All staff must understand protocol for the treatment and evaluation of patients, therefore a pilot study may be useful to help the staff. Regular meetings with all participants to help with enthusiasm will be useful for ensuring the trial still runs with maximum efficiency. Furthermore, the principal statistician being involved in organisational matters can help detect problems others may not see.

References

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