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SAFER 2 DATA ANALYSIS PLAN

Trial Title

SAFER 2: Support and Assessment for Fall Emergency Referrals 2

Trial Summary

Care of older people who fall: evaluation of the clinical and cost effectiveness of new protocols for emergency ambulance paramedics to assess and refer to appropriate community based care

Trial Details

Trial Registration: ISRCTN 60481756
Chief Investigator: H.A. Snooks, Swansea University

Revision History

Revision Date	Release	Summary of Changes	Changes Made by
09/2009	1.0	Initial version	WYC
03/2010	1.1	Revised to include economic analysis	WYC
04/2010	1.2	Revised to include qualitative analysis	WYC
05/2010	1.3	Revised with protocol	HS
07/2010	1.4	Revised randomisation, PGI, non-consenter & non-respondent analyses	WYC
09/2010	0.4	Version numbers revised by DMEC 20/07/10	JP
02/2012	0.5	Revised with protocol	AJW
03/2012	0.6	Revised with protocol	SG
05/2012	0.7	Revised economic & qualitative analyses	BA
07/2012	0.8	Revised for DMEC meeting on 24/07/12	AJW & ITR
05/2013	0.9	Further revisions	SG, IH, AJW

Approvals

This document requires the following approvals. A signed copy should be placed in the project files.

Name	Signature	Title	Date of Issue	Version

Distribution

This document has been distributed to:

Name	Title	Date	Version
SAFER 2 DMEC		20-07-2010	1.4
SAFER 2 DMEC		24-07-2012	0.8
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Section 1: SUMMARY AND OVERVIEW

SAFER 2 is a pragmatic cluster randomised controlled trial (CRT) with a qualitative component, involving 25 ambulance stations from three UK centres (namely, the East Midlands, London, and Wales)[1]. 223 paramedics taking part in the study have recruited approximately 6000 patients who call 999 following a fall. Half of the participating stations have been randomly allocated to an intervention group, and paramedics based at these stations deliver care to older people who have fallen according to new protocols which allow emergency ambulance paramedics to assess and refer patients to appropriate community based care. The control group comprises the remaining stations, and paramedics based at these deliver normal care.

Randomisation of stations to groups was carried out in accordance with the principles outlined in WWORTH SOP24 Randomisation[2]; specifically, randomisation was undertaken *after* paramedics in study stations had volunteered to participate (thus avoiding possible selection bias), and used centre and the number of eligible calls attended (based on data from 2009) as stratification variables. Clinical relevance is related to, but not determined by, the criterion of one event avoided (or incurred) in ten, which was the clinically significant effect size used in the sample size calculation. The calculated sample size for binary outcomes (whether an event occurred or not) is also adequate for a statistical assessment of the observed differences in times to the first event in the intervention and control group.

This analysis plan for SAFER 2 has been developed using appropriate CONSORT (www.consort-statement.org) statements and checklists, including those relating to cluster trials and patient-reported outcomes.

Section 2: TRIAL OBJECTIVES

The overall aim of this trial is to assess the benefits and costs to patients and the NHS of a complex intervention comprising education, clinical protocols and pathways enabling paramedics to assess older people who have fallen and refer them to community-based falls services when appropriate. Specific objectives are to:

1 Compare outcomes, processes and costs of care between intervention and control groups:
   - a patient outcomes: rate and pattern of subsequent emergency healthcare contacts or deaths, for any reason and for falls; health related quality of life (HRQoL); psychological status (especially fear of falling); and change in place of residence
   - b processes of care: pathway of care at index fall; subsequent healthcare contacts; ambulance service operational indicators and protocol compliance including clinical documentation
   - c costs of care: provided by NHS and personal social services; incurred by patients and carers in seeking care;

2 Estimate wider system effects of the introduction of the intervention on ambulance service performance and costs;
3 Understand how patients experience the new health technology;
4 Identify factors which facilitate or hinder the use of the intervention;
5 Inform the development of methods for falls research, especially outcome measures recommended for trials of interventions for older people who fall [3]

Section 3: DATA COLLECTION & HANDLING

3.1 Data Sources & Collection

Our primary outcome is "further emergency healthcare contacts (999 call or Emergency Department (ED) attendance or hospital admission) or death for any reason and for falls per recruited faller, and time to first contact or death" for six months following the index call. This CRT does not approach participants at the point of treatment, because they may be in distress and unable to give informed consent, but seeks instead retrospective consent to follow up through routine medical records and by postal questionnaire. We planned to follow-up all our patients anonymously in order to achieve the primary outcome for our target sample size. In Wales, arrangements for this process are already in place through the existing SAIL (Secure Anonymised Information Linkage) Database, and our application for permission through the Information Governance Review Panel has been granted. We applied to the NIGB Ethics and Confidentiality Committee for permission to follow-up our patients anonymously through the Information Centre in England and permission has been granted for this process. Conditional to this permission, people who have clearly dissented to identifiable follow-up must be excluded from the study. For clarity, if a patient has at any time declined to be part of the study (either in returning a consent form or orally on the telephone) they will be removed from the study.

3.2 Sample Size and Statistical Power

We made the conservative estimate that trial patients have about 50% chance of making another emergency contact within six months; in the absence of intra-cluster correlation (ICC), a sample of 4190 evaluable participants yields 90% power, when using two-sided 5% significance level, of detecting a change in this chance from 50% to <45% or to >55%. The analogous outcome in the SAFER 1[4] trial indicated an ICC of zero in clusters of participants seen by paramedics from the same ambulance station. To be conservative, we therefore allowed for an ICC of 0.002, and sought 251.6 (calculated from 0.998*4190/{25-0.002*4190}) participants per ambulance station, making a total sample size target of 6290.

However, actual recruitment is slightly lower, at 5939 participants, and we will lose approximately 1000 patients that decline to be part of the study. Furthermore, previous experience suggests that we shall also lose about 10% of the remaining patients from analysis because we shall not be able to match them with their routine electronic data on contacts with the NHS. Hence we expect the recruited sample of 5939 participants to yield only 4400 suitable for accurate information linkage. With an ICC of 0.002 and equal cluster sizes, this expected evaluable sample size corresponds to 3260 independent participants, which, in turn, equates to approximately 80% statistical power. In short, the cumulative loss in recruitment, and from dissenting and un-matched patients will reduce the statistical power of SAFER 2 from a conservative 90% to the traditional 80%, even allowing for more intra-cluster correlation than observed in the SAFER 1[4] trial.

3.3 Missing Data

General Principles

As per WWORTH SOP28 Statistics[5], we shall adopt a consistent approach to missing data relating to both effectiveness and cost-effectiveness except where individual outcome measures require some variation in that approach. We shall exclude participants without follow-up data, and, for each variable, summarise the frequency of missing data, which directly influences the sample size in, and hence the statistical power of, some analyses. If there is reason to suspect that data are not Missing Completely At Random (MCAR), the trial statistician and chief investigator will discuss the findings. If there is no reason to suspect that data are not MCAR, we shall use appropriate imputation methods to mitigate the problem of missing data.

Internal imputation of HRQoL data at a particular data collection point

None of the questionnaires (SF-12, derived SF-6D, or Modified Falls Efficacy Scale (mFES)[6]) has an official algorithm for imputing individually missing answers. Some patients may have particular reasons for missing some of the questionnaire items, and it is unlikely that a plausible model for conditional Missing At Random can be established even on a case-by-case basis. Nevertheless, to minimise missing values and use available information, any such missing values within patient interviews will be completed by imputation[7] within the reduced dataset of individual responses to questions in the three measures, using the regression or expectation maximization (EM) algorithms of the Missing Value Analysis module within SPSS. Scale scores will then be calculated according to the relevant instructions for the measure. The use of multiple imputation methods will be considered if the incidence of missing data is high.

External imputation of HRQoL data scores

If a participant is dead at the data collection point, the SF-6D score will be taken as zero. To avoid outliers, SF-12 and mFES scores will be taken as the minimum value observed for that measure in the relevant treatment group

Otherwise, missing summary scale and subscale scores will be imputed by regression from all available values of that score at other data points and the allocated treatment group. Further predictors (eg gender, age, current hospitalisation) may be included, unless they are already used as covariates in the main analysis

If any potential predictor other than study group has an F value of less than 1 (that is, it increases the standard error of the prediction) it will be removed from the list of predictors and the prediction recalculated.

Missing Health Economic data

Addressing the problem of missing data may involve employing Mean Imputation (that is, assigning a mean value to the respondents with missing data) or Regression Imputation (that is, using regression models to provide estimates of missing data from complete data, when the missing data is part of a multivariate data set). The usual method for dealing with censored data relating to costs will be to employ the weighted cost method with known cost histories[8].

3.4 Withdrawals

Patients can withdraw from the study whenever they wish, and do not have to give a reason, although any reasons given must be documented. Their subsequent treatment will not be affected in any way. Patients may also withdraw from the questionnaire element of the study but be retained for other follow up. Any patients lost must be traced and documented whenever possible.

Wherever possible, data missing because of withdrawal will be imputed from available data.

Section 4: LINKS BETWEEN OBJECTIVES & OUTCOMES

4.1 Trial Objective 1 ‘Compare costs, processes and outcomes of care between experimental and control groups’

Objective 1a Patient Outcomes

1	Number of further reported contacts or deaths	**[primary outcome]**
2	Time to the first reported contact or death	**[primary outcome]**

Primary outcomes will be analysed using the hierarchy of outcomes (comprising 999 calls, ED attendances, emergency admissions, and death) established in SAFER1[4].

3 Injuries related to further falls **[secondary outcome]**

This will be summarised by cross-tabulation of the numbers and proportions in each study group, split by types of injuries.

4 Health-related Quality of Life **[secondary outcome]**

This is measured by SF-12 and derived SF-6D, and will be assessed and summarised at one month and six months.

5 Satisfaction **[secondary outcome]**

This is measured by the Quality of Care Monitor, and will be assessed and summarised at one month.

6 Psychological status **[secondary outcome]**

This is measured by the mFES, and will be assessed and summarised at one month and six months.

7 Change in place of residence at six months **[secondary outcome]**

Objective 1b Processes of Care

1 Pathway of care **[secondary outcome]**

This is measured by health and social care contacts associated with the index fall and during follow-up period, split by types of contacts and adjusted by covariates.

2 Ambulance service operational indicators **[secondary outcomes]**

These comprise episode of care and job cycle times, adjusted by covariates.

3 Protocol compliance **[secondary outcome]**

This will be measured by a series of data items related to protocol compliance (such as the completion of clinical documentation; referral processes).

Objective 1c Cost of Care [secondary outcome]

This objective is addressed by estimating and comparing the resources utilised in both groups, adopting a 'bottom-up approach' from the perspective of the NHS, personal social services, and patients and their families. Specifically:

1 Estimation of costs of providing the intervention

Data relating to direct costs to the NHS will be assessed using data logged as a part of routine practice and from resource utilisation recording sheets, together with reference to patient records and discussions with relevant finance staff. Resources used will be translated into costs using relevant published unit costs.

The number of non-conveyances will be logged, and potential impact on costs to the ambulance service and hospital emergency departments estimated.

Further, the additional costs to community services will be documented and costs using relevant published unit costs.

2 Costs to patients and families

Patients and their families will complete a self-administered questionnaire specifically designed for this study but based on other instruments catalogued within the Database of Instruments for Resource Use Management (www.dirum.org).

Further, data on the use of the health service and social services resources will be collected for each patient using a combination of paramedic records and routine hospital records (for hospital events). Data relating to social services costs will be derived from discussion with relevant social services departments

4.2 Trial Objective 2 'Estimate wider system effects of the introduction of the intervention on ambulance service performance and costs'

We consider this objective two parts.

Objective 2a Wider effect on operational indicators

Ambulance service operational indicators **[secondary outcomes]**

Response times across the study catchment and surrounding areas during the trial period will be compared to pre-trial response times and 'rest of service' response times (adjusted for pre-trial differences) in order to identify any knock on or halo effects.

Objective 2b Wider effect on Costs of Care [secondary outcome]

Consequences of the scheme for the wider NHS and social services (eg ED attendances, inpatient admissions, GP consultations, out-of-hours GP contacts, NHS Direct contacts, social services utilisation) will be estimated using a combination of routine data sources, discussions with staff from relevant departments (eg social services) and from responses to patient completed questionnaires that highlight service contacts and utilisation..

Further, the time spent by ambulance staff with patients and the nature of their involvement will be documented so as to determine the direct cost of patient care, cost of patient transportation and other costs – reflecting travel, time spent at ED discharging patients and so on.

4.3 Trial Objective 3 'Gain an in-depth understanding of how the intervention is experienced by patients'

This objective is addressed using face-to-face semi-structured interviews conducted in co-operation with a carer or older person present at time of fall. Qualitative interviews to be undertaken with patients who: experienced a fall; were recruited to the trial; seen by an intervention paramedic and agreed to the interview. This will include patients: who were taken to ED; referred to a falls service; and patients who were neither taken to the ED nor referred to a falls service.

The aims of the interviews are to explore:

- Patient experience of ambulance service
- Patient experience of those seen by a falls service
- Patient health since fall
- Patient satisfaction with treatment

4.4 Trial Objective 4 'Understand how the intervention is delivered in practice, identifying factors which enable or hinder its use'

This objective is addressed using focus groups carried out with intervention paramedics 'pre' and 'post' trial. Focus groups will be carried out by two researchers, one to lead discussions and one to take notes and enable the linkage of texts to speakers as well as concerning other details, such as points of consensus or disagreement, issues that drew strong emotional responses such as anger, fear or anxiety.

The aims of the focus groups are to explore:

- Paramedics views and attitudes toward the new intervention
- Any preconceptions about the new way of working

- Factors which enable the use of the new referral pathway
- Factors which hinder the use of the new referral pathway

4.5 Trial Objective 5 'Inform the development of methods for falls research in relation to outcomes assessment'

We shall compare mFES scores with SF-12 component scores and derived SF-6D scores as recommended by Prevention of Falls Network Europe (ProFaNE)[9] group to establish construct validity. We shall assess predictive validity by comparing mFES scores with the mean number of further falls and time to first subsequent fall.

Section 5: MAIN ANALYSES

5.1 Statistical Analysis

This will conform to principles outlined in WWORTH SOP28 Statistics [5]; specifically, the primary analysis will be by 'treatment allocated', reflecting the pragmatic nature of the trial design where patients are cared for by paramedics based at ambulance stations randomly allocated to deliver intervention or control care.

Primary outcomes comprise a hierarchy relating to further emergency healthcare contacts for falls, as measured by contacts with the 999 service, Emergency Department (ED) or emergency admission to hospital for a further fall, or deaths within six months of the index fall. Important predictors that may affect triage decisions and outcomes, including the distance between incidents and EDs at index fall, patient age and gender, patterns of presentation (eg, whether out-of-hours or not) will be considered as covariates, and included in statistical modelling. We shall also take account of potential confounders such as the sequence of base stations (and their trial allocation) from which paramedics attend patients who fall more than once. The principles used in analysing primary outcomes also apply to quantitative secondary outcomes.

Required analyses include: logistic regression (for binary outcomes); cross-tabulations and risk ratios (for categorical outcomes); and survival analysis, including Cox's proportional hazards models[10], (for measurement outcomes, such as times to events). Primary outcomes will also be jointly analysed using methods developed for recurrent event analysis[11-14]. Repeated observations will be analysed in two ways: as 'repeated measures'; and summarised by "area under curve" of HRQoL measures per patient.

Where appropriate, multilevel modelling will be used to estimate clustering effects for stations or centres. The exact number of levels in models will be determined using statistically significant changes in likelihood ratio tests according to the principle of parsimonious parameterisation. Potential covariates to be included in models will be tested; those with an F value of less than 1 (that is, they increase the standard error of the estimate) will be excluded and the analysis recalculated. Binary covariates where almost all cases (>90%) are in one category will also be excluded.

Residual diagnostics will be used where analyses assume Normality; if the distributions of residuals are markedly non-normal, data transformation or bootstrapping will be considered. Residual analysis will be used to identify outliers; identified outliers will be excluded and the analysis updated. Wherever possible, outcome descriptions, summaries and comparisons will be expressed in accordance with appropriate CONSORT (www.consort-statement.org) guidelines, including estimates with 95% confidence intervals (allowing two-tailed tests at the 5% significance level).

5.2 Health Economic Analysis

This will estimate costs of providing the new intervention, and consequences for the NHS (for instance, ED attendances, inpatient admissions) and personal social services. Data on the use of the health service resources will be collected for each patient using routine ambulance service and hospital records. Costs will then be calculated using unit-costs estimated through a micro-costing study within the trial. Direct costs to the NHS will be assessed using data logged as a part of routine practice and from resource utilisation recording sheets, together with reference to patient records and discussions with relevant finance staff.

SF6D scores (derived from SF12 scores) will also be used to estimate the quality adjusted life years (QALYs) gained from the intervention, and an incremental cost-per-QALY calculated. These ratios will be presented along with their associated Cost-effectiveness Acceptability Curves (CEAC). Sensitivity analyses will be undertaken to assess the robustness of results to changes in the configuration of the intervention and other health service costs. We aim to publish economic results alongside clinical results where possible (for instance, in the BMJ format of pairs of companion papers).

The Senior Trial Economist is responsible for the health economic analysis, which will generally adopt approaches employed in the main analysis of clinical data. Specifically: .

- Analysis will be by 'treatment allocated' when generating baseline findings, with inclusive analysis by treatment received or exclusive analysis of treatment per-protocol being used for sensitivity analysis when also undertaken in reporting clinical findings
- Addressing uncertainty by applying bootstrapping for CEACs and confidence intervals[15-17].
- Using a range of time-horizons to estimate the effectiveness and cost-effectiveness of the intervention.
- Applying appropriate discount rates to costs and benefits, as required by NICE; applying appropriate threshold Incremental Cost-effectiveness Ratios (ICER), such as the £20,000 and £30,000 thresholds used by NICE, in cost-per-QALY calculations.

5.3 Qualitative Analysis

All interviews and focus groups, with the permission of participants, will be recorded and transcribed. As this is a team-based project involving collection of data in multiple sites, maintaining consistency in data collection and transcription is crucial. The qualitative analysis co-ordinator will set up a data management system consisting of instructions on converting raw data to computer files (in the form of a transcription protocol), organising data storage, data archiving steps and a data management checklist. The transcription protocol will ensure that standard conventions are adopted throughout the transcription process, and that a standard presentation format is used. Each transcript will be quality assured by the relevant researcher.

Following transcription, participants in the paramedic and service provider focus groups will be given the opportunity to review the anonymised transcripts and state whether they agree with the contents or wish to amend their quotes.

The data will be analysed thematically using the framework analysis approach for applied policy research [18]. This is a systematic, dynamic and transparent method of analysis, which generates themes from the original accounts of participants [19]. In the analysis the data is sifted, charted and sorted in accordance with key issues and themes using five steps: familiarisation; identifying a thematic framework; indexing, charting; and mapping and interpretation.

All data analysis will be carried out independently by two researchers, who will then meet to discuss and agree final coding and interpretation. Analysis will be conducted using NVivo. When reporting the results, we will ensure that the anonymity of responders is preserved and that no quote can be attributed to a particular individual.

Section 6: INTERIM & FURTHER ANALYSES

Patients will be recruited over a 15 month period and followed up for six months. The trial will end and be analysed after the last six month follow-up contact with any patient in the trial. No formal interim analyses of the trial outcomes, and no subgroup analyses, are planned within the trial.

6.1 Non-Consenter Analysis

Study patients will be compared with eligible patients who have not consented to the study in terms of age, gender, date and time of index call, on-scene time, main condition code and disposition by appropriate significance tests.

6.2 Non-Respondent Analysis

Study patients who have returned the study questionnaire will be compared with those who have not return the questionnaire by the same parameters of the non-consenter analysis. In addition, those responding to the questionnaire will also be compared to those not returning the questionnaire in terms of the primary outcomes.

6.3 Sensitivity Analyses

Subject to resources, we will carry out further appropriate sensitivity analyses, some identified as the main analyses proceed. These will include a comparison between identifiable data retrieved from hospitals and those retrieved through the anonymous data sources (where experience with SAFER1[4] indicates that a good or perfect match between anonymised records and study participants should be possible in 90% of cases); consideration of patterns of referral to falls services; and analyses based on further refined definitions of the intervention group – for instance, excluding participants ineligible for falls service referral.

Section 7: REPORTING & RELATED ISSUES

The SAFER 2 DMEC will receive immediate notification of all SUSARs, and summaries of current trial data. This will allow the DMEC to monitor trial progress, and request unblinded comparisons where they have cause for concern. The DMEC may then make a final decision to modify or terminate the trial, as specified in its terms of reference.

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