QUEEN'S UNIVERSITY BELFAST

Statistical Analysis Plan

Version 1

Claire Carswell

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1 Background and Design

In order to establish the effectiveness of arts-based interventions rigorous randomised controlled trials are the most robust method of evaluation. However there are difficulties associated with randomised controlled trials, particularly around recruitment and retention of participants (Donovan *et al.*, 2014). This is exacerbated in palliative care trials where participation rates under 50% are common (Hanson *et al.*, 2015). Trials in nephrology, the most under-researched field of internal medicine, also experience problems retaining participants (Palmer *et al.*, 2011). The reasons for these low recruitment and retention rates are multi-factorial, including ethical implications of working with patients who have an end-stage illness, the emotional distress and burden placed on participants who may experience severe symptoms such as fatigue, pain and nausea (Hanson *et al.*, 2015).

Methodology in arts-based intervention research needs to be considered due to the lack of randomised controlled trials (Bungay *et al.*, 2014; Boyce *et al.*, 2017). Arts-based interventions meet the Medical Research Council's description of a complex intervention (Medical Research Council, 2009), in that it involves several interacting components that can impact on implementation, evaluation and the context in which it is delivered. There is a tendency of complex interventions to fail to show a significant effect in randomised controlled trials (Levati *et al.*, 2016). This absence of detectable effect may not result from an ineffective intervention, but instead could be a consequence of the logistical difficulties in standardising and evaluating complex health interventions in an experimental process (Medical Research Council, 2009). Consideration needs to be given to optimising the intervention and the trial process, such as recruitment procedures and randomisation, for the context in which the intervention will be delivered. To address these issues Levati *et al.* (2016) recommend feasibility studies. These focus on real world implementation during the development of the intervention and research design, by involving key stakeholders throughout each stage of the process and 'in vivo' exploration of problems that occur with implementation and trial processes during feasibility testing.

When exploring staff perceptions of arts-based interventions, the focus in the literature is on how the intervention impacts the patients, with fewer studies examining the effect of the intervention on healthcare staff themselves (Bungay *et al.*, 2014; Boyce *et al.*, 2017). Due to the unique nature of the clinical working environment it is particularly important to consider the acceptability of an intervention for healthcare staff (May, 2013) . The acceptability for patients must also be taken into consideration. If an effective intervention is burdensome or

non-engaging, patients will not participate and therefore not experience potential benefits (May, 2013). In order to evaluate whether an intervention is acceptable in practice, a process evaluation must be conducted. Process evaluations provide a detailed understanding of complex interventions by examining their implementation, mechanism of impact and context (Moore *et al.*, 2015).

The All Party Parliamentary Group report on the Arts for Health and Wellbeing (All-Party Parliamentary Group on Arts Health and Wellbeing, 2017) reflects the lack of cost-effectiveness analysis and economic evaluations conducted for arts-based interventions (Craemer, 2009). Cost-effectiveness analyses are important as they are the basis of decision making for health intervention recommendations by National Institute for Health and Care Excellence (NICE) (Ogden, 2017). In order to ensure that the effectiveness of an intervention can guide healthcare policy, economic evaluations and cost-effectiveness analysis are needed to establish justification for funding. However, due to the absence of economic evaluations for arts-based interventions implemented within hospital settings, it is important to explore the best methods for conducting such cost-effectiveness analyses.

The study will consist of four phases and will utilise a mixed-method design. Phase 1 will consist of the development of the intervention, phase 2 will involve a quantitative feasibility randomised controlled trial (RCT), phase 3 will involve a qualitative process evaluation and phase 4 will involve feasibility testing for an economic evaluation.

The RE-AIM mixed methods framework (Forman et al., 2017) will be used to guide the research process. The framework outlines the core aspects of a complex intervention that should be explored to enhance the generalisability of findings (Glasgow and Estabrooks, 2018). The core aspects include the intervention's reach, effectiveness, adoption, implementation and maintenance. Not all RE-AIM objectives can be met within a feasibility study, for example, the maintenance of the intervention over time. However the framework will be used to inform research questions, data collection and outcomes appropriate for a feasibility study.

1.1 Inclusion/Exclusion criteria

1.1.1 Inclusion criteria patients

- Age 18 or over
- Able and willing to participate

- Receiving haemodialysis

1.1.2 Exclusion criteria patients

- Unable to provide consent or participate due to lack of capacity or physical ability
- Under the age of 18
- Non-English speaking patients who are unable to understanding verbal or written communication without the aid of an interpreter.

1.1.3 Inclusion criteria healthcare staff

- A member of the multidisciplinary team, including nurses, healthcare support workers, doctors, dietitians, social workers and counsellors.
- Have had experience with the intervention.
- Have worked in a clinical renal setting for more than 3 months

1.1.4 Exclusion criteria healthcare staff

- Not a member of the multi-disciplinary team
- Have not experienced the intervention, either directly or in passing.
- Have not worked in the clinical renal setting for more than 3 months

Justifications for these inclusion and exclusion criteria are contained within the protocol.

2 Outcome measures

2.1 Primary outcome measures

- Phase 2 (Feasibility RCT): Feasibility of recruiting and retaining participants for a randomised controlled trial as determined by proportion of target sample size recruited and retained over 3 month follow up.
- Phase 3 (Process Evaluation): Acceptability of the intervention for patients and healthcare staff as reported during semi-structured interviews and focus groups.
- Phase 4 (Feasibility economic evaluation): Feasibility of using the Patient Resource Use Log to capture healthcare use data as determined by proportion of participants who complete the Patient Resource Use Log and proportion of missing data.

2.2 Secondary outcome measures

- Phase 2: Exploration of demographic factors that may influence recruitment and retention.

- Phase 2: Time taken for recruitment, data collection and data analysis.
- Phase 2: Acceptability of clinical outcome measures (Hospital Anxiety and Depression Scale (HADS), Kidney Disease Quality of Life – Short Form 36 (KDQOL-SF36)) as determined by completion rates and proportion of missing data.
- Phase 3: Perceptions of clinical outcome measures (Hospital Anxiety and Depression Scale, Kidney Disease Quality of Life – Short Form 36) from qualitative interviews and focus groups
- Phase 3: Experiences of implementation of the arts-based intervention from qualitative interviews and focus groups.
- Phase 4: Feasibility of using the EQ-5D-5L to calculate cost-utility values as determined by proportion of participants who complete the EQ-5D-5L and proportion of missing data.
- Phase 4: Cost of the intervention in terms of material price.

3 Data

3.1 Management of data sets

Data will be collected and analysed by the PhD student responsible for this study, with oversight and supervision from the PhD supervisory team and guidance from a University Statistician. Quantitative data will be analysed using Statistical Package for the Social Sciences (SPSS v 24), while qualitative data for the process evaluation will be digitally recorded and transcribed verbatim prior to data analysis. All data will be stored in accordance with the Data Protection Act (2018) participants will be provided an anonymous code and identifiable information will be removed from the qualitative data to maintain confidentiality. A more detailed overview of data storage and management is included in the study protocol, and an overview of the timing of data collection can be seen in Table 1.

Table 1	Screening Baseline	Post intervention/ 3 weeks	6 weeks	3 months (12 weeks)
PATIENT				
Informed Consent	X			
Inclusion/Exclusion Criteria	X			
Demographic Data	X			
9-point Clinical Frailty Scale	x			
KDQOL-SF36	x	x	x	x
EQ-5D-5L	x	x	x	x
HADS	x	x	x	x
Patient Service Use Log	x	x	x	x
Diabetes and diabetic comorbidity check	x	x	x	x
Qualitative interview	At one point during study			
HEALTHCARE PROFESSIONALS				
Informed Consent	x			
Inclusion/Exclusion Criteria	x			
Qualitative interview	At one point during study			

4 Sample Size Calculation

4.1 Sample size for feasibility RCT and economic evaluation

A sample size of 30 is recommended by the NIHR's Research Design Service for the estimation of a parameter, such as sample size, recruitment or attrition rate, for a definitive randomised controlled trial, although they recognise that advice varies from 24 to 50 participants. Due to the increased risk of identifying a statistically significant result with larger sample sizes, and practical limitations of a small, single centre study, a sample size of 30 was selected for the feasibility RCT. A university statistician was consulted who confirmed that a sample of 30 was an appropriate sample size to meet the objectives of the study. A more comprehensive overview of the sample size decision is available in the study protocol.

4.2 Sample size for Process Evaluation

Approximately 13 patients will be recruited into the process evaluation. Simulations have shown that this sample size of 10 should identify 80% of problems within a complex intervention (O'Cathain *et al.*, 2014), while data saturation is likely to be reached at 12 interviews on average (Guest *et al.*, 2006). The principle of 10 + 3 for data saturation outlines that a minimum of 10 interviews should be conducted, followed by at least 3 consecutive interviews that present no new findings (Francis *et al.*, 2010), therefore a sample of 13 patients will be recruited for semi-structured interviews. Approximately 5 healthcare staff will be recruited into each focus group, with a proposed total of 3 focus groups (Schneider *et al.*, 2009). The dialysis unit in which the study is taking place is relatively small, therefore the focus groups will be limited by the amount of staff available who meet the eligibility criteria and the requirement to produce a manageable amount of data for the time limitations of the study (Carlsen and Glenton, 2011; O'Cathain *et al.*, 2014). However, these are approximate sample sizes, and data collection will continue until data saturation is reached. The researcher will provide the participants with a consent form prior to commencement of the focus group (Appendix 6). Data saturation will be determined when there is no new data being found from which additional themes can be developed (Guest *et al.*, 2006).

5 Analysis Principles

Baseline demographic and clinical data will be analysed using descriptive statistics. Categorical data will be presented as frequencies and percentages, while continuous data will be presented as means and standard deviations

Primary quantitative outcomes: Recruitment, participation and retention rates will be reported and presented in a CONSORT flow diagram (Eldridge *et al.*, 2016). Data on patients who were eligible for recruitment, who consented to participation, who completed the study, and completion of the Patient Resource Use Log will be presented as proportions and rates.

Secondary quantitative outcomes: Chi squared tests will be conducted to establish whether the experimental and control group differ significantly in baseline demographic and clinical data. Completion of the KDQOL-SF36, HADS and EQ-5D-5L will be presented as proportions and rates. A cost consequence analysis will be used to provide a comparative overview of differences in costs and outcomes of participants in the experimental and control group.

Qualitative outcomes: The semi-structured interviews and focus groups will be recorded and transcribed verbatim. Inductive thematic analysis will be used to analyse the data collected. Investigator triangulation, method triangulation and data source triangulation will be used to ensure validity of the identified themes. A more comprehensive description of qualitative analysis is available in the study protocol.

Clinical outcomes: Exploratory inferential statistics will be conducted, but no conclusions on the effectiveness of the intervention will be made from the results. Independent t-tests (or the non-parametric equivalent Mann-Whitney U) will be conducted to compare the scores of the experimental group and control group. The majority of arts-based intervention research involves pre-and-post-test designs; therefore a repeated measures t-test (or the non-parametric equivalent Wilcoxon Matched Pairs test) will also be conducted to compare the mean scores of the experimental before and after receiving the intervention. An analysis of variance will be conducted to explore any potential sub-group analysis that may be relevant within a future RCT. The amount of time taken to conduct this analysis will be reported to inform feasibility.

6 Analysis details

6.1 Recruitment and follow-up patterns

Recruitment and follow-up patterns will be presented in a CONSORT flow diagram and an overview of eligibility, reasons for non-recruitment, and reasons for withdrawal will be recorded and included in the flow diagram.

6.2 Patient Baseline Characteristics

The median (interquartile range) will also be presented for skewed data

- Age, mean (SD)
- Gender, no.(%)
- Education, no.(%)
- Dialysis vintage, mean (SD)
- Ethnicity, no.(%)
- Clinical Frailty Scale, no.(%)
- Number of co-morbidities, mean (SD)
- KDQOL-SF36
- EQ-5D-5L
- HADS
- Patient Resource Use Log

6.3 Clinical Outcome Measures

- Week 3, 6, and 12: KDQOL-SF36
- Week 3, 6, and 12: EQ-5D-5L
- Week 3, 6 and 12: HADS

6.4 Patient Resource Use Log (Administered at baseline, week 3, 6 and 12)

- Home care worker (nhs), no.(%) and mean (95%CI)
- Home care worker (paid), no.(%) and mean (95%CI)
- Meals on wheels (nhs), no.(%) and mean (95%CI)
- Meals on wheels (paid), no.(%) and mean (95%CI)
- Other care visits, no.(%) and mean (95%CI)
- GP visits at surgery, no.(%) and mean (95%CI)

- -Duration of visit, mean (95%CI)
- GP telephone consultations, no.(%) and mean (95%CI)
- GP Home visit, no.(%) and mean (95%CI)
- Calls to out-of-hours, no.(%) and mean (95%CI)
- Visits to out-of-hours, no.(%) and mean (95%CI)
- Nurse visits at surgery, no.(%) and mean (95%CI)
- Nurse telephone consultation, no.(%) and mean (95%CI)
- Community/district nurse home visit, no.(%) and mean (95%CI)
- Social worker visits, no.(%) and mean (95%CI)
- Occupational therapist visits, no.(%) and mean (95%CI)
- Other visits, no.(%) and mean (95%CI)
- Visits to A&E, no.(%) and mean (95%CI)
- Visits to hospital clinic (kidney related), no.(%) and mean (95%CI)
- -Duration of visit, mean (95%CI)
- Visits to hospital clinic (not kidney related), no.(%) and mean (95%CI)
- -Duration of visit, mean (95%CI), mean (95%CI)
- Admissions to hospital/ residential unit, no.(%) and mean (95%CI)
- -Duration of stay (days), mean (95%CI)

7 Additional information

7.1 Supervision

The study will be overseen by the supervisory team consisting of Dr Helen Noble, Professor Joanne Reid and Mr Ian Walsh. Supervision will occur approximately every two weeks to provide oversight and guidance during data collection, data analysis and interpretation. Regular e-mail and telephone support is also available.

7.2 Advisory Group and User Involvement

The study protocol and arts-based intervention has been developed in conjunction with an inter-disciplinary Advisory Group for the research project. The Advisory Group includes healthcare staff representatives from the haemodialysis unit at Antrim Area Hospital, including the principle investigator at the site and consultant nephrology, Dr Robert Mullan, and the unit's research nurse Michael Matthews; an artist representatives from Arts Care Northern Ireland, Andrea Spencer; the CEO of Arts Care Northern Ireland, Dr Jenny Elliot;

three patient representative from the Northern Ireland Kidney Patient Association, Jean Michelo, Christopher Johnston and William Johnston; a representative from University of Florida school of Arts in Medicine, Jenny Baxley-Lee; the manager of Community Wellbeing in the Northern Trust, Mr Hugh Nelson; the renal counsellor for the Northern Trust, Elizabeth Weatherup; and a statistician from Queen's University Belfast, Dr. Helen McAneney. This group will meet approximately every 3 months, both face to face and virtually, in order to provide guidance throughout the research project.

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