Achieving Quality and Effectiveness in Dementia Using Crisis Teams (AQUEDUCT): A Randomised Controlled Trial of a Resource Kit for Teams Managing Crisis in Dementia

Statistical Analysis Plan

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Trial registration(1): ISRCTN

The following people have reviewed the Statistical Analysis Plan and are in agreement with the contents(6)				
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Abbreviations

Abbreviation	Description
AE	Adverse Event
AQUEDUCT	Achieving Quality and Effectiveness in Dementia Using Crisis Teams
BPSD	Behavioural and Psychological Symptoms of Dementia
BPT	Best Practice Tool
CEBM	(Oxford) Centre for Evidence-Based Medicine
CI	Chief Investigator (Professor Martin Orrell)
CMHT	Community Mental Health Team
COVID-19	(Novel) Coronavirus Disease 2019 (WHO nomenclature)
CRF	Case Report Form
CRHTT	Crisis Resolution and Home Treatment Team
CRN	Clinical Research Network
CRT	Crisis Resolution Team
CSQ-8	Client Satisfaction Questionnaire – 8 item version
DMC	Data monitoring committee
EM-CRN	East Midlands Clinical Research Network
EQ-5D-5L	EuroQoL quality of life questionnaire – 5 + 5 item version
FM	Fidelity Measure
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GHQ-12	General Health Questionnaire – 12 item version
HRA	Health Research Authority
HTP	Home Treatment Package
HTT	Home Treatment Team
IMH	Institute of Mental Health, Nottingham
IQR	Interquartile Range
ITT	Intention to Treat
MAR	Missing At Random
MCID	Minimum Clinically Important Difference
MLM	Multilevel Modelling
MRC	Medical Research Council
NHS	National Health Service
NIHR	National Institute for Health Research
NottsHC	Nottinghamshire Healthcare NHS Foundation Trust
PMG	Programme Management Group
PPI	Patient and Public Involvement
PSG	Programme Steering Group
PSS	Personal Social Services
QALY	Quality-Adjusted Life Year
R&E	Research and Evidence Department
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RK	Resource Kit
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SD	Standard Deviation
SHIELD	Support at Home – Interventions to Enhance Life in Dementia
TAU	Treatment As Usual
TMCD	Team Managing Crisis in Dementia
TMG	Trial Management Group
TSG	Trial Steering Group
UoN	University of Nottingham
UWES	Utrecht Work Engagement Scale
WAAQ	Work Acceptance and Action Questionnaire
WP	Work Package

Add or delete rows as applicable

Changes from protocol

The table below details changes to the planned analyses in the SAP compared to the protocol which after discussion with the TMG are not considered to require a protocol amendment.

Protocol version and section	Protocol text	SAP version and section	SAP text	Justification
				Include information on reason, date of decision and how documented

Amendments to versions(4)

Version	Date	Change/comment	Statistician

Additional contributors to the SAP (non-signatory) (5)

Use this section to acknowledge other individuals who have made a significant contribution to the SAP.

Name	Trial role	Job Title	Affiliation

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1. Introduction

This document details the rules proposed and the presentation that will be followed, as closely as possible, when analysing and reporting the main results from the study titled "Achieving Quality and Effectiveness in Dementia Using Crisis Teams: A Randomised Controlled Trial of a Resource Kit for Teams Managing Crisis in Dementia". These analyses will assess the efficacy and safety of an online Resource Kit (RK) for use by Teams Managing Crisis in Dementia in comparison with the standard management and will be included in the clinical study report.

The purpose of the plan is to:

- Ensure that the analysis is appropriate for the aims of the trial, reflects good statistical practice, and that interpretation of a priori and post hoc analyses respectively is appropriate.
- Explain in detail how the data will be handled and analysed to enable others to perform or replicate these analyses.

Additional exploratory or auxiliary analyses of data not specified in the protocol may be included in this analysis plan. This analysis plan will be made available if required by journal editors or referees when the main papers are submitted for publication. Additional analyses suggested by reviewers or editors will be performed if considered appropriate. This should be documented in a file note.

Amendments to the statistical analysis plan will be described and justified in the final report of the trial and where appropriate in publications arising from the analysis. **Health economic** and **qualitative analysis** plans are beyond the scope of this document.

1.1 Background and rationale (7)

Synopsis of trial background and rationale including a brief description of research question and brief justification for undertaking the trial (All instruction, highlighted in blue will be removed in final version SAP)

To be brief, previous research undertaken as part of the AQUEDUCT programme found that Teams Managing Crisis in Dementia (TMCDs) vary greatly in terms of team names, eligibility criteria, staffing, duration of contact with the person with dementia, and interventions available. The AQUEDUCT research programme aims to provide a Best Practice Model against which TMCDs can evaluate their provision of crisis care for people with dementia; teams can then use an online Resource Kit to strengthen their provision of care. A definitive randomised trial is now needed to compare use of this Resource Kit by TMCDs (intervention arm) against Treatment As Usual (TAU) by TMCDs in the control arm.

1.2 Objectives (8)

Description of specific objectives or hypotheses,

Research hypothesis

The null hypothesis is that there is no difference in the effect of care management with online Resource Kit (RK) and usual care management. The alternative hypothesis is that there is a difference between the two groups.

Study objectives

Primary objectives

1. The primary objective is to Evaluate impact of use of the Resource Kit (RK) by TMCDs on psychiatric hospital admissions for people with dementia in the geographical catchment area covered by the TMCD.

Secondary objectives

Secondary objectives are to:

1. Evaluate impact of use of the Resource Kit (RK) by TMCDs on acute/general hospital admissions for people with dementia in the geographical catchment area covered by the TMCD.
2. Evaluate impact of use of the Resource Kit on those receiving input from the TMCD using the RK, (people with dementia and carers of people with dementia).
3. Evaluate impact of use of the Resource Kit on TMCD practitioners using the RK.

Exploratory objectives

Explore the possible mechanism of action of the RK via comparison of Best Practice Tool (BPT) scores for TMCDs in the intervention arm across the duration of the study period.

2. Study methods

2.1 Trial design (9)

Brief description of trial design including type of trial (e.g., parallel group, multi-arm, crossover, factorial) and allocation ratio and may include brief description of interventions

The trial is a two arm, randomised, parallel-group, treatment as usual (TAU) controlled trial. Treatment allocation is a 1:1 ratio. TMCD are randomised to either RK arm or matched TAU control.

2.2 Randomisation & Blinding (10)

Randomization details, e.g., whether any minimization or stratification occurred (including stratifying factors used or the location of that information if it is not held within the SAP). Specify who were blinded to group assignment (e.g. investigators, assessors, participants, statistician); of those who are unblinded (e.g. data manager and the data monitoring committee) indicate extent of contact with study participants

1. The randomisation process is described in full within the clinical trial protocol. Details of the randomisation method are held securely within the statistics master file. Once consent has been obtained from each Team Managing Crisis in Dementia (TMCD), the TMCD will be entered onto a web-based randomisation system and be randomly assigned to one of two arms, either RK (using the Resource Kit) or TAU (treatment as usual) with equal opportunity. The allocation will be determined by a computer generated pseudo-random code using random permuted blocks of varying size, stratified by the population size (number of people with dementia) in each TMCD catchment area. The block size will not be disclosed. Patients, carers, outcome assessors and statisticians will be blinded to TMCD arm allocation until the data analysis is completed.

2.3 Sample size (11)

Full sample size calculation or reference to sample size calculation in protocol (instead of replication in SAP). better Copy protocol.

The sample size calculation was based on scoping information collected in earlier stages of the AQUEDUCT research programme, which showed the average hospital admission count per TMCD catchment area over a 6 month period to be 33. Following consultation with stakeholders, it was agreed that a 20% reduction represented the minimum clinically important difference (MCID); therefore, 15 TMCDs will be required in each of the two study arms (30 in total) to detect a 7 point mean admission count difference between arms with 90% power at a two-tailed 0.05 significance level [1], assuming the count of hospital admissions follows a Poisson distribution. It is anticipated that no TMCD will withdraw from the study and that NHS Trusts will provide the required hospital admissions data for each TMCD; thus, it is unlikely that the number of TMCDs required will be influenced by lost information due to TMCD withdrawal. Software Stata 16 was used for this power analysis.

2.4 Framework(12)

Superiority, equivalence, or noninferiority hypothesis testing framework, including which comparisons will be presented on this basis. Specifying the framework of a trial refers to its overall objective to test the superiority, equivalence or non-inferiority of one intervention from another. The SAP should clearly specify the framework for each outcome or provide a global statement. Primary and secondary might have different framework. i.e equivalence for primary but superiority for 2ndary outcome.

The AQUDUCT trial protocol stated the objectives is to evaluate the impact of use of RK on psychiatric hospital admissions for people with dementia in the geographical catchment area covered by the TMC as primary objective, the secondary objectives include evaluating the impact of RK using by TMCD on acute/general hospital admissions for people with dementia in the geographical catchment area covered by the TMCD, on service user in including both patients with dementia and career, on TMCD practitioners, therefore both primary and secondary outcomes are testing for superiority of RK used by TMCD over care with TAU management.

2.5 Statistical interim analyses and stopping guidance (13)

- Information on interim analyses specifying what interim analyses will be carried out and listing of time points
- Any planned adjustment of the significance level due to interim analysis
- Details of guidelines for stopping the trial early

There is no formal interim analysis planed.

2.6 Timing of final analysis (14)

Timing of final analysis, e.g., all outcomes analysed collectively or timing stratified by planned length of follow-up

The final analysis will be performed once the last patient's final outcome data were available.

2.7 Timing of outcome assessments (15)

Time points at which the outcomes are measured including visit "windows"

The schedule of study procedures for all data collection is given in the Table 1 in section 5.1. Briefly, all outcome measure will be collected at baseline during randomisation time and 6 month follow-up time.

3 Statistical Principals

3.1 Confidence intervals and P values (16-18)

- Level of statistical significance(16)
- Description and rationale for any adjustment for multiplicity and, if so, detailing how the type 1 error is to be controlled(17)
- Confidence intervals to be reported(18)

All applicable statistical tests will be 2-sided and will be performed using a 5% significance level; No planned adjustment for multiplicity as the study has only one primary outcome [2]. All confidence intervals presented will be 95% and two-sided."

3.2 Adherence and protocol deviations (19)

- Definition of adherence to the intervention and how this is assessed including extent of exposure
- Description of how adherence to the intervention will be presented
- Definition of protocol deviations for the trial
- Description of which protocol deviations will be summarized

Compliance is assessed based on ****. It is defined as: ****. Descriptive statistics on the percent compliance will be summarized by randomisation group

The following are pre-defined major protocol violations with a direct bearing on the primary outcome: *****
Protocol deviations are classified prior to unblinding of treatment. The number (and percentage) of patients with major and minor protocol deviations will be summarised by treatment group with details of type of deviation provided. The patients that are included in the ITT analysis data set will be used as the denominator to calculate the percentages. No formal statistical testing will be undertaken.

Note: "compliance & protocol adherence to be updated in future version"

3.3 Analysis populations (20)

Definition of analysis populations, e.g., intention to treat, per protocol, complete case, safety

The intention-to-treat population will include all randomised TMCD catchment area data, regardless of their eligibility, according to the treatment arm they were randomised to receive.

4 Trial population

4.1 Screening data (21)

Reporting of screening data (if collected) to describe representativeness of trial sample
The number of TMCD screened will be presented in CONSORT diagrams.

4.2 Eligibility (22)

Summary of eligibility criteria

The number of ineligible TMCD randomised, if any, will be reported, with reasons for ineligibility and presented in CONSORT diagrams.

4.3 Recruitment (23)

Information to be included in the CONSORT flow diagram

A CONSORT flow diagram will be used to summarise the number of TMCDs who were:

- assessed for eligibility at screening
    - eligible at screening
    - ineligible at screening for the following reason(s):
    - TMCD is not defined by service/NHS Trust as having a role in dementia mental health crisis management;
    - TMCD does not meet the following definition for mental health crisis: *providing urgent mental health assessment and intervention for people with dementia in the community*;
    - A major service reorganisation is planned over the study period or is anticipated in the near future;
    - NHS Trust and/or TMCD are not able to demonstrate capacity and capability to complete required research activities;
    - TMCD is co-located with another TMCD taking part in this study, (sharing the same site is acceptable but sharing the same office is not);
    - TMCD shares immediate management structures with another TMCD taking part in this study, (sharing a management structure above the level of TMCD leader is acceptable but sharing a TMCD leader is not);
    - Core clinical staff for TMCD do not operate separately from another TMCD taking part in this study – this includes a requirement that core clinical staff must not engage in clinical cross cover with another TMCD taking part in this study;
    - TMCD shares core administrative staff with another TMCD taking part in this study;
    - If a TMCD leader who has been exposed to the intervention becomes lead for a TMCD in the control arm of the RCT, that latter TMCD will then be excluded.
- eligible and randomised
- received the randomised allocation
- lost to follow-up due to TMCD withdrawal from trial
- discontinued the intervention as TMCD wished to return to usual practice
- randomised and included in the primary analysis

4.4 Withdrawn/follow-up (24)

- Level of withdrawal, e.g., from intervention and/or from follow-up
- Timing of withdrawal/lost to follow-up data
- Reasons and details of how withdrawal/lost to follow-up data will be presented

The level of consent withdrawal will be tabulated (classified as “consent to continue follow-up and data collection” “consent to continue data collection only”, “complete – no further follow-up or data collection”).” This will be presented in CONSORT diagram format rather than as a table, with numbers and reasons for withdrawal and/or exclusion from analysis given at each stage. The numbers (with reasons) of losses to

follow-up (drop-outs and withdrawals) over the course of the trial will be summarised by treatment arm."

4.5 Baseline patient characteristics (25)

- List of baseline characteristics to be summarized
- Details of how baseline characteristics will be descriptively summarized

TMCD service users' and TMCD practitioners' background information and individual demographic characteristics will be described with respect to age, gender, ethnicity, diagnosis, and time since diagnosis for people with dementia, with respect to age, gender, ethnicity, and relationship to person with dementia for carers, and with respect to age, gender, ethnicity, job title and banding, and whole time equivalence specifically in TMCD plus in NHS overall for TMCD practitioners; this will be done both overall and separately for the two randomised groups. The details of descriptive statistics are reported in 5.2.1. Tests of statistical significance will not be undertaken for baseline characteristics; rather the clinical importance of any imbalance will be noted [3].

5 Analysis

5.1 Outcome definitions (26)

List and describe each primary and secondary outcome including details of:

- Specification of outcomes and timings. If applicable include the order of importance of primary or key secondary end points (e.g., order in which they will be tested)
- Specific measurement and units (e.g., glucose, hbA1c [mmol/mol or %])
- Any calculation or transformation used to derive the outcome (e.g., change from baseline, QoL score, Time to event, logarithm, etc.)

Information of primary and secondary outcomes are summarised in table 1.

Table 1: Summary of the outcome measures

Information Covered	Measure/Data Collection	note
Primary outcome		
Hospital admissions for people with dementia to mental health beds, in the geographical catchment area of the TMCD (as defined by postcode)	• *Psychiatric hospital admissions in TMCD catchment*	to be collated and reported at baseline and 6 month follow-up point for preceding time period (6 months duration each)
Secondary outcome		
Hospital admissions for people with dementia to acute beds, in the geographical	• *Acute/general hospital admissions in TMCD catchment area*	to be collated and reported at baseline and 6 month follow-up point for preceding time period (6 months duration each).

catchment area of the TMCD (as defined by postcode)		Precise details of local acute NHS Trust(s) relevant to TMCD geographical catchment area to be provided by NHS Trust R&E Department covering TMCD; subsequent data collection will be responsibility of AQUEDUCT research team
Assessment of satisfaction with service input received by people with dementia and carers, measured using a standardised scale	• Client Satisfaction Questionnaire (CSQ-8) –NB – people with dementia (where possible) and carers can complete measure up to 6 weeks post discharge from TMCD	CSQ-8 to be completed once post discharge from the TMCD (to a total n = 450 across all 30 TMCDs) by people with dementia (where possible) and carers identified by TMCD practitioners; responsibility of TMCD research co-ordinators
Post-training Self-administered Assessment on the RK	• Assessment of understanding post RK training, completed by TMCD practitioners	Responsibility of AQUEDUCT research team
Assessment of general health of people with dementia and carers, measured using a standardised scale	• General Health Questionnaire (GHQ-12) –NB – people with dementia (where possible) and carers can complete measure up to 6 weeks post discharge from TMCD	GHQ-12 to be completed once post discharge from the TMCD (to a total n = 450 across all 30 TMCDs) by people with dementia (where possible) and carers identified by TMCD practitioners; responsibility of TMCD research co-ordinators
Assessment of work acceptance and action by TMCD practitioners, measured using a standardised scale	• Work Acceptance & Action Questionnaire (WAAQ) – completed by all TMCD practitioners at baseline and at 6 month follow-up point	WAAQ to be completed individually by all practitioners in TMCD; responsibility of TMCD research co-ordinators
Assessment of work engagement by TMCD practitioners, measured using a standardised scale	• Utrecht Work Engagement Scale (UWES) – completed by all TMCD practitioners at baseline and at 6 month follow-up point	UWES to be completed individually by all practitioners in TMCD; responsibility of TMCD research co-ordinators

Assessment of general health of TMCD practitioners, measured using a standardised scale	• General Health Questionnaire (GHQ-12) – completed by all TMCD practitioners at baseline and at 6 month follow-up point	GHQ-12 to be completed individually by all practitioners in TMCD; responsibility of TMCD research co-ordinators
Assessment of sickness absence for TMCD practitioners	• TMCD practitioner sickness absence to be collated for all TMCD practitioners at baseline and at 6 month follow-up point for preceding time period (6 months duration each)	TMCD practitioner sickness absence to be collated and reported by TMCD research co-ordinators
Best Practice Tool scores for TMCDs in the intervention arm across the duration of the study period	• BPT – completed by TMCDs in intervention arm only at baseline and at 6 month follow-up point	BPT to be completed as a joint exercise by members of TMCD; responsibility of TMCD research co-ordinators

5.2 Analysis methods [27]

- What analysis method will be used and how the treatment effects will be presented
- Any adjustment for covariates
- Methods used for assumptions to be checked for statistical methods
- Details of alternative methods to be used if distributional assumptions do not hold, e.g., normality, proportional hazards, etc.
- Any planned sensitivity analyses for each outcome where applicable
- Any planned subgroup analyses for each outcome including how subgroups are defined

All analyses will be conducted on an Intention-To-Treat (ITT) basis [4].

5.2.1 Summary of primary and secondary outcomes analysis

All patient demographic and outcome measures will be summarised by arm across measuring times, with n (non-missing sample size), mean, standard deviation, median, maximum and minimum for continuous variables, the frequency and percentages (based on the non-missing sample size) of observed levels for all categorical measures.

5.2.2 Analysis of primary outcome

Poisson regression with binary arm status as an explanatory variable will be implemented to quantify the treatment effect estimates and precision on mental health hospital admission, the offset will be the number of dementia patient population within each TMCD catchment area. An over-dispersion check will be performed and a negative binomial regression model will be used if there is evidence that the outcome variance is greater than the mean. The Poisson model could be written as

$$y_i \sim \text{Poisson}(\mu_i)$$
$$\ln(\mu_i) = \beta_0 + \beta_1 \text{arm}_i + \ln(\text{offset}_i)$$

with μ_i is the expected value of Mental Health hospital admission y_i for each TMCD i, arm_i is the allocation status for TMCD i, offset_i is the number of dementia patients papulation in each TMCD i catchment area. β_1 is the treatment effect estimate. The analytical unit is TMCD.

5.2.3 Sensitivity analyses of primary outcome

Poisson regression will be performed with binary arm status as an explanatory variable, baseline number of mental health service admission as offset [5].

5.2.4 Analysis of secondary outcomes

Treatment effect on general hospital admission will be analysed using similar Poisson regression used for primary analysis. Treatment effect estimates on individual TMCD practitioner, person with dementia and carer outcome measures will be explored via multilevel modelling (MLM), with the TMCD as the level two analytical unit [6]; baseline measures will be included as covariates [3, 7]. Skewed continuous outcome variables will be transformed for MLM, and nonlinear MLM will be performed for categorical outcomes. Sensitivity analysis for secondary outcome measures will be conducted on data with missingness imputed to check the robustness of treatment effects estimates sensitive to influence of missingness. The two level linear model could be written as

$$y_{ij} = \beta_{0j} + \beta_1 \text{arm}_j + \beta_2 \text{baseline}_{ij}$$
$$\mu_{0j} \sim N(0, \sigma^2_{\mu_0})$$
$$e_{ij} \sim N(0, \sigma^2_e)$$

with y_{ij} is the observed outcome measure change from baseline for individual i from TMCD j catchment area, β_1 is the treatment effect estimate. μ_{0j} is the departure of TMCD j mean y_{ij} from overall mean, following normal distribution with mean =0 and variance= $\sigma^2_{\mu_0}$. e_{ij} is the residual term unexplained by model and follow a normal distribution with mean =0 and variance= σ^2_e. If TMCD level variance $\sigma^2_{\mu 0}$ estimate is not statistically significant, single level regression model will be performed instead to quantify the treatment effect estimate.

5.2.5 Analysis for exploratory aim

The before- and after- comparison will be made on the Best Practice Tool (BPT) scores for TMCDs in the intervention arm, to aid exploring the possible mechanism of action of the RK.

5.3 Missing data(28)

Reporting and assumptions/statistical methods to handle missing data (e.g., multiple imputation)

Missing values will be checked and reported across both arms for all outcome measures collected for all participant groups. For the primary outcome psychiatric

hospital admissions information, as NHS Trusts will provide the data, it is unlikely there will be any missingness. For secondary outcomes collected from people with dementia, carers and TMCD practitioners, multilevel logistic regression will be used to explore the influence of group status and baseline measures on outcome data absence with the TMCD as the level two analytical unit. These results will be used to inform missing value imputation using analytical modelling under missing at random (MAR) assumptions [8, 9]; Stata and REALCOM software will be used to perform multiple imputations via analytical model. MCMC procedure setting include burn-in length=5000, chain length=5000, a thinning of 10 and non-informative priors for all parameters. Twenty imputed datasets will be generated initially with possible imputing number increasing after checking imputation performance [10]. Results from imputed dataset will be combined using Rubin's imputation rules to produce a pooled treatment effect estimate (95% CI) and a pooled p-value for the test of null hypothesis of no treatment effect [9].

5.4 Additional analyses/exploratory analysis (29)

Details of any additional statistical analyses required, e.g., complier-average causal effect analysis

There is no planned additional analysis and other exploratory analysis.

5.5 Harms & Adverse events (30)

- Sufficient detail on summarizing safety data, e.g., information on severity, expectedness, and causality;
- details of how adverse events are coded or categorized; how adverse event data will be analysed, i.e., grade 3/4 only, incidence case analysis, intervention emergent analysis

The number (and percentage) of patients experiencing each AE/SAE will be presented for each treatment arm categorised by severity **[11]**. For each patient, only the maximum severity experienced of each type of AE will be displayed. The number (and percentage) of occurrences of each AE/SAE will also be presented for each treatment arm. No formal statistical testing will be undertaken.

5.6 Statistical software (31)

Details of statistical packages to be used to carry out analyses

The analysis will be carried out using Stata, REALCOM and other packages such as MLwiN if necessary. All the software will be the then latest version available in University of Nottingham (UoN) when study data is ready for analysis. All the data will be stored in UoN secure server and analysed in UoN computers. All the data and analytic code will be archived as per instruction from study PI Professor Martin Orrell who will be the data custodian for this study.

6 References (32)

- References to be provided for nonstandard statistical methods
- Reference to Data Management Plan
- Reference to the Trial Master File and Statistical Master File
- Reference to other standard operating procedures or documents to be adhered to

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