Care Homes Independent Pharmacist Prescribing Service (CHIPPS):

A cluster randomized controlled trial to determine both its effectiveness and cost-effectiveness

The CHIPPS RCT : a definitive randomised controlled trial

Statistical Analysis Plan

Version 1.0

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SAP REVISION HISTORY

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CHIPPS Statistical Analysis Plan	1.0	03-02-2020

ABBREVIATIONS

ADE	Adverse Drug Event
AE	Adverse Event
CCG	Clinical Commissioning Group
CHUMS	Care Homes' Use of Medicines Study (CHUMS) 2009
CQC	Care Quality Commission
CRF	Case Report Form
DBI	Drug Burden Index
DMC	Data Monitoring Committee
FIML	Full Information Maximum Likelihood
GEE	Generalised Estimating Equation
HRA	Health Research Authority
ICC	Intra-class Correlation Coefficient
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention-to-Treat
NCTU	Norwich Clinical Trials Unit
NRES	National Research Ethics Service
PCP	Pharmaceutical Care Plan
PIP	Pharmacist Independent Prescribers
RA	Research Associate
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
UKCRC	UK Clinical Research Collaboration
WP	Work Package

1.0 Administrative Information

Sponsor :	South Norfolk Clinical Commissioning Group
ISRCTN :	17847169, registered 15th December 2917
NRES :	East of England Cambridge Central: 17/EE/0360 Scotland A REC: 17/SS/0118
UKCRC Trials Unit :	Norwich Clinical Trials Unit
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2. Introduction

2.1 Background and Rationale

In 2012, care homes in the UK provided accommodation for almost half a million residents in beds registered for either residential or nursing care. The transfer from one's own home to a facility which provides 24-hour care is usually as a result of being unable to live independently, mainly due to a deterioration in health. Consequently, care home residents are generally frail, have multiple morbidities and are prescribed a significant number of regular medicines. Unfortunately, age-related complex morbidity renders them particularly vulnerable to medication problems and errors. The Care Quality Commission identifies the management of medicines as one area of care in care homes that regularly requires review and continues to fall below the expected standards.

The landmark UK-based Care Homes Use of Medicines Study (CHUMS) published in 2009 observed 256 residents in 55 care homes. Almost 70% of residents experienced at least one medication error on any given day. One hundred residents (39.1%) were identified as having one or more prescribing errors. For 20%, no strength or route of medicine was specified; for almost one quarter, a medicine was deemed to be unnecessary. Dose/strength errors accounted for 14.4% of all errors; occasions when a prescribed medicine had not been given, accounted for 11.8%, of all errors. Out of 218 potentially harmful medicines which required biochemical monitoring, 32 (14.7%) had an error. This was most often a failure to request blood tests. Fifty-seven (22.3%) residents had a total of 116 administration errors (i.e. errors on the drug round), nearly half of which were omissions and more than one fifth the wrong dose. Carers were observed using inappropriate techniques when administering medicines such as inhalers. Problems with medicines ordering and stock holding led to omissions. Hospital discharge letters were also criticised for being unclear, delayed, missing or not adequately incorporated into the residents' clinical records. The researchers noted that the main method of communication regarding medicines was the medication administration chart and this was often inaccurate.

Many of these medication-related problems were also reported in a systematic review by Alldred et al [1] which considered interventions to optimise prescribing for older people in care homes. Problems highlighted were prescription of medicines that were no longer indicated, medicines which interacted with concurrent medication, sub-optimal doses, inadequate monitoring and inappropriate duration. The

inappropriate prescription of anti-psychotic medicines in care homes is well documented and is known to be related to poor quality of life, falls and increased mortality. Other medicines with potential for long-term harm that are known to be prescribed inappropriately in care homes are benzodiazepines, non-steroidal anti-inflammatory drugs and proton pump inhibitors. Consequently, effective interventions are needed to monitor and discontinue therapy. Inadequate monitoring can result in sub-optimal dosing, over-treatment or the unintentional treatment of side effects that have been incorrectly identified as a new symptom that requires further treatment.

The CHUMS report proposed that the fundamental failing in care homes was the lack of a healthcare professional with overall continuing responsibility for medicines management and recommended that a pharmacist should adopt this role working with a lead general practitioner (GP) within each home. The Department of Health (DH) Immediate Action Alert arising from CHUMS required primary care organisations, GPs and community pharmacy contractors to establish effective joint working strategies to address the identified concerns. The resultant predominant model of care is that of a pharmacy team undertaking full medication reviews in care homes on a yearly or biannual basis. Two recent Cochrane reviews conducted by Hughes and Alldred [1, 2] suggest that this model is sub-optimal and more effective approaches to medicines optimisation in this population are required.

Recent changes in UK legislation, enabling suitably trained pharmacists to prescribe, provides an opportunity for pharmacist independent prescribers (PIPs) to assume the proposed central role in the care home environment. Evidence from the UK, led by Bond and involving Wright and Holland, suggests that pharmacist independent prescribers can prescribe safely and provide patient benefit. It would also be similar to that mandated in the USA, whereby a pharmacist is required to be an integral part of the care home team where they develop, implement and monitor individualised medicines-focused (pharmaceutical) care plans. However they are not responsible for prescribing.

We propose that a suitable model for care homes is a PIP, who would assume responsibility for appropriate medicines management, monitoring and authorising repeat prescriptions, and overall management of medicines. Such a PIP would use pharmaceutical care plans (PCPs) to communicate prescribing decisions and plans between members of the care team. PCPs state the indication for each medicine, monitoring requirements (efficacy and side effects), review date and additional relevant information e.g. related policies or guidance on administration method (for a full list of all the data that will be collected in the PCP). The PIP would develop PCPs when establishing the service, liaising with the care home staff, residents and GP where necessary. They would then review the PCP on a monthly basis to confirm efficacy, ensure that adverse drug reactions are identified and managed, the ongoing need for therapy is considered and that monitoring is requested in a timely manner. PCPs would be regularly updated, reviewed and integrated within medical practice and care home records. The PCP would be a detailed record of all resident-related medication activities undertaken by the PIP and act as an aide memoire for the provision of future care. To address concerns identified within the CHUMs study, the PIP could additionally assume responsibility for managing transfer of medicines information between care locations, observe medication administration and actively ensure that stock levels are adequate to prevent missed doses.

Before introducing this innovative model of care, in addition to determining its optimal content, we anticipate a large number of logistical and professional barriers may need to be overcome. We have therefore developed a programme of work comprising six work packages (WPs). This statistical analysis plan relates solely to WP6 (RCT with internal pilot) which was informed by work undertaken during the earlier work packages (using the literature and views of stakeholders (care home managers, staff,

residents and relatives, GPs and pharmacists), development of a needs based PIP training, and a non-randomised feasibility study) to determine the final service specification and training package for the PIPs.

2.2 Objectives

The objectives for the CHIPPS 'full' RCT are:

(i) to describe and quantify the clinical effectiveness of the intervention: pharmacist independent prescribers (PIP) assuming responsibility for medicines management of elderly residents in care homes
(ii) to estimate the cost-effectiveness of the intervention

The primary hypothesis is:

i) In care home residents, the fall rate per person at 6 months will be less for those residents receiving care under the PIP model, compared to those residents receiving usual care.

Secondary hypotheses are:

ii) The PIP model will be superior to 'usual care' in terms of cost-effectiveness.

iii) The PIP model will be superior to 'usual care' in terms of quality of life, physical functioning, reducing hospitalisation and mortality.

This Statistical Analysis Plan (SAP) is concerned with the analytical methods addressing the first objective, relating to the clinical effectiveness, of the CHIPPS RCT.

3. Methods

3.1 Trial Design

The CHIPPS clinical trial is a two group, parallel, cluster randomised, controlled trial conducted in care homes for older people and associated GP practices.

3.2 Randomisation

The study recruitment is based upon 'triads' which act as the unit of randomisation, and defines the 'clusters' in the data analysis. A recruited triad consists of 1 GP practice plus 1 PIP plus residents from at least one care home, with a target mean of 20 residents per triad. Following recruitment of the triad, it is randomised to either the intervention (PIP) or control ('usual care') arms. Randomisation is performed using a web-based electronic randomisation system integrated into the study database. The randomisation lists are generated by the Data Management Team in Norwich CTU and are stratified by recruiting region (four in total: Aberdeen, Belfast, Leeds and Norwich).

3.3 Sample Size

Recruitment aimed for 880 participants (440 in each arm) which will detect a decrease in fall rate from 1.50 per individual over 6 months to 1.178 with 80% Statistical Power. This assumes that the number of clusters available will be 44, with a mean of 20 participants from each, a loss rate of no more than 20% and an intra-class correlation coefficient (ICC) for the primary outcome of falls of 0.05 or less.

These assumptions are based upon data from the CAREMED trial (unpublished data), which estimated a fall rate of 1.5 per individual over a 6 months period. The detectable difference (from 1.5 to 1.178) is a relative reduction of 21% which is half that detected within a UK based pharmacist led medication review service provided to care homes.

Data from the CAREMED trial indicated a mortality rate of 33% and further loss to follow-up of 5% over 12 months. Thus, a reasonable estimate of total losses due to mortality or other reasons over 6-months would be 20%. However, we will use data, where possible, up to the point at which someone withdrawals from the study (either voluntarily, or otherwise). Therefore, those lost to follow-up, for whatever reason, should contribute some information on falls rate to the study analysis.

3.4 Framework

The CHIPPS clinical trial is a superiority trial based upon a frequentist statistical inferential approach.

3.5 Interim analyses and stopping guidance

No formal efficacy interim analyses were planned. However, summaries of recruitment rates, withdrawal rates, etc. were conducted at intervals during the study and made available to the Data Monitoring Committee (DMC) in formal reports.

3.6 Timing of final analysis

The main analyses will be carried out at a time after all data have been collected and entered for the final participant for the 6 month follow-up and pertinent data queries resolved. This is anticipated to be April 2020.

3.7 Timing of outcome assessments

All participants are invited to undergo screening, baseline and post-randomisation follow-up assessments at 3 and 6 months. The primary time point for analysis is 6 months post-randomisation.

4. Statistical Principles

A frequentist statistical approach will be used. All hypothesis testing will use the conventional two-side 5% statistical significance level. Confidence intervals for parameter estimates will be at the corresponding 95% level.

Analyses will be carried out by the trial statistician blinded to group identity, (i.e. whilst aware of the grouping, unaware to which group is intervention and which control 'subgroup' blind), where possible.

No formal analyses will be undertaken until the statistical analysis plan, this document, is approved by the Data Monitoring Committee (DMC).

The primary analysis will be on the 'Intention-to-Treat' population (ITT), defined as including all subjects randomised and within the group to which they were allocated, irrespective of treatment actually received or adherence to intended treatment.

A 'Per Protocol' (PP) analysis will also be completed using participants in the intervention group deemed to have received the PIP intervention as intended. The 'Per Protocol' sample will consist of all those in the control arm and in the intervention arm in a care home which had a minimum of three months exposure to the intervening PIP. It is possible that the estimates from the PP analysis will be biased as this sample will not necessarily maintain the baseline balance induced by randomization. Should the PP analysis be inconsistent with the ITT analysis this possibility needs consideration and explicit acknowledgement.

In the case of an inconsistent conclusion between the two analyses, where the ITT analysis yields no evidence of a beneficial effect but the PP analysis does, a further exploratory, 'dose' analysis will be carried out. In this case, a model will be constructed where the exposure to the PIP intervention is included (in weeks) and the association between outcome and exposure length in estimated. For the control arm, this will necessarily be zero weeks and will vary in the intervention arm.

5. Trial Population

5.1 Trial Eligibility

Residents are considered eligible for enrolment in the trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

5.1.1 Prescribing Independent Pharmacist (PIP)

Inclusion criteria:

- registered as a pharmacist independent prescriber
- following CHIPPS study training, can demonstrate to their mentor and independent GP assessor competence to deliver service specification
- ability to work flexibly and commit a minimum of 16 hours a month to deliver the service for six months

Exclusion criteria:

- substantive employment with the community pharmacy (branch/store) which supplies medicines to the care home with which the PIP would work, to protect against conflict of interest
- already providing an intensive service to the care home, e.g. a monthly visit (or more frequently), and provision of intensive medication focused services

5.1.2 GP Practices

Inclusion criteria:

- GP practice must manage sufficient care home residents to support recruitment of the target of approximately 20 eligible participants.

5.1.3 Care Homes

Inclusion criteria:

- Care Quality Commission (CQC) in England, Care Inspectorate in Scotland or Regulation and Quality Improvement in Northern Ireland, registered specialism as caring for adults over 65
- primarily caring for residents over 65 years
- associated with a participating GP practice (i.e. one or more residents registered with a participating practice)

Exclusion criteria:

- care homes which receive regular (e.g. a monthly visit or more frequently), from a pharmacist, providing another intensive medication focused services
- care homes which receive regular (e.g. a monthly visit or more frequently), from another health care professional, providing another intensive medication focused services
- care homes which are currently under formal investigation with Care Quality Commission (CQC) in England, Care Inspectorate in Scotland or Regulation and Quality Improvement in Northern Ireland
- care homes that are participating in any other study likely to affect the outcome of the CHIPPS trial (e.g. Falls intervention study, Rehydration study, etc.)

5.1.4 Care Home Residents

Inclusion criteria:

- under the care of the participating GP practice
- aged 65 years or over
- currently prescribed at least one regular medication
- they or their appropriate representative is/are able to provide informed consent/assent
- permanently resident in care home (not registered for respite care/temporary resident)

Exclusion criteria:

- currently receiving end of life care, [equivalent to yellow (stage C) of the Gold Standards Framework prognostic indicator]
- have additional limitations on their residence (e.g. held securely)
- participating in another intervention research study

5.2 Screening data

Screening information will be summarised within the 'participant flow' diagram and study exit numbers, with reasons, tabulated. No information is available for non-consenting subjects, thus no comparison will be made with participants.

5.3 Recruitment and participant flow

Patient recruitment and flow will be illustrated through a diagram as indicated in the Appendix, following standard 'CONSORT' practice.

5.4 Withdrawal / follow-up

The study involves four different participant types consenting or agreeing to participate, in the study and therefore potentially withdrawals from the study: the PIPs, GP practices, care homes and care home residents. Withdrawal at any level will be reported upon within group.

5.5 Baseline participant characteristics

A comparison will be made between the intervention and control groups at baseline to assess comparability. The baseline characteristics to be summarized will be all baseline demographic variables, all primary and secondary outcomes measured at baseline, and potential prognostic variables. This between group comparison will include characteristics of the three members of the cluster 'triad' in addition to participating care home residents.

No formal hypothesis testing will be carried out but descriptive statistics (according to assumed distribution) will be presented.

6.0 Analysis

6.1 Outcome definitions

Outcome data on residents will be collected at baseline, three months (falls and EQ-5D only) and at the end of the intervention period of six months, using standard, validated approaches.

6.1.1 Primary Outcome

The primary efficacy outcome is the fall rate at 6 months post initiation of the intervention. A fall in this period is defined as an event labelled as such in the care homes' fall records. No additional sources of information are being used to capture these data. A CHIPPS research will identify such events directly from the care homes' fall records.

6.1.2 Secondary Outcomes

- Fall rate per person in past three months at 3 months
- Drug Burden Index (DBI) at 6 months
- Proxy EQ-5D-5L (quality of life) at 3 months and 6 months
- Face to face self-reported EQ-5D-5L (only applicable for participants with capacity) at 3 months and 6 months
- Proxy Barthel Index (physical functioning) at 6 months follow-up
- Hospitalisation rate per person during 6 month follow up
- Mortality rate during 6 month follow-up

6.1.3 Further Outcomes

The following process outcomes are collected per participating resident:

- Number of medications derived from the medication records during the 9 months prior to intervention and over the 6 months follow-up period.
- Use of antipsychotic drugs (a class of medicines used to treat psychosis and other mental and emotional conditions), derived from the medication records. In addition, this will be included in calculating the DBI.
- Duplicate drugs: information about duplicate drugs (both true drug duplicates and therapeutic drug duplication) is collected in the intervention group (only) by the PIPs and will be used to describe the intervention.

6.2 Analysis Methods

The primary analysis will compare the PIP intervention group with the 'usual care' control group with respect to fall rate per person, at 6 months post randomisation. This will use the intention to treat principle: i.e. all participants will be followed up for data collection irrespective of any intervention received or the level received and will be analysed according to group allocation rather than intervention received.

The number of falls over 6 months will likely follow a Poisson distribution and a between group comparison to estimate the difference in falls will be made using a Poisson Regression model. This model will include:

- baseline fall rate (baseline outcome value);
- treatment group (intervention or control);
- recruiting region (as a random factor);
- home status (residential versus nursing; prognostic variable);
- baseline Barthel Score (prognostic variable);
- baseline DBI Score (prognostic variable);
- baseline Charlson Morbidity Index (prognostic variable).

An 'offset' will be included in the model, which will be the logarithm of follow-up time. This will allow the inclusion of individuals lost to follow-up prior to 6 months.

The unit of analysis will be the individual participant but, due to the study design incorporating 'clustering' these unit outcomes are likely to be correlated. Therefore, a Generalised Estimation Equation (GEE) approach will be used for parameter estimation. The Poisson assumption will be assessed with 'fit' statistics and, if appropriate, a Zero Inflated Poisson (where a larger frequency of zero falls occurs than would be expected under the assumption of a Poisson distribution), or a Poisson model with an over-dispersion term will be considered. As the GEE approach does not use a maximum-likelihood based estimation, the likelihood based 'fit' statistics are not useful. Therefore, the QIC (Quasi-likelihood under the independence model criterion), proposed by Pan [3], analogous to the Akaike Information Criterion, will be used. The model with the lower (better) value will be used.

Secondary analyses will be conducted using an analogous GEE model, with an appropriate change to the link and error term, depending upon the nature of the outcome of interest. The fall rate at 3 months and hospitalization rate will be modelled using a Poisson model, with zero inflated if necessary. Mortality will be modelled with a Cox Regression Model, using time from consent until death (or otherwise censored). Robust Sandwich estimates of the standard errors will be used to adjust for the 'clustering' within care homes. The remaining secondary outcomes, EQ-5D-5L, the Barthel Index and the Drug Burden Index, will be modelled with the assumption of a Normal distribution (i.e. a Normal Error and the identity link). Transformations of these outcome variable will be considered in the case that the error distribution assumption does not appear Normal (e.g. a logarithmic transformation of skewed data to fit a Normal distribution). No formal tests will be used to assess the Normal distribution but residual plots and summary statistics (such as the skewness statistic) will be examined. The explanatory variables for these models will be the same as those used for the primary model, together with the outcome value at baseline where available.

The estimate of the between group difference will be provided with a 95% confidence interval and tested at the 5% significance level.

6.3 Missing Data

The approach to analysis, i.e. using rate of falls, should preclude the necessity for any formal statistical method to impute, or otherwise mitigate against, missing data. All participants will contribute information to the primary outcome unless withdrawn from the study prior to any follow-up information, i.e. very shortly after time of entry. This exception is likely to apply to a very small proportion of participants. However, it is possible that individuals with very short time periods of observation could lead to extreme estimates of fall rates, which are highly influential data. For example, a participant may have one or two falls recorded within an available observation period of just a few days. Therefore, a sensitivity analysis will be carried out where individuals with less than 10 days of observation are not included in the analysis.

For the secondary outcomes of fall rate by 3 months and hospitalization an identical approach outlined above will be used. For the secondary outcome of survival, incomplete individuals can be included in the analytical model as censored observations. For the remaining secondary outcomes, where at least 50% of participants are available for analysis, multiple imputation (using 20 imputed data sets) will be used with standard errors for parameter estimates constructed using Rubin's rules.

6.4 Safety Data

For the CHIPPS study, a Serious Adverse Event (SAE) is defined as either a death or an unplanned admission to hospital. An SAE within the PIP intervention group deemed related to the intervention is considered a Suspected Unexpected Serious Adverse Reaction (SUSAR). The number of SAEs will be tabulated and compared between the two groups, using a GEE as described above. Three models will be constructed: for all SAEs, for Deaths and for Admissions. The number of SUSARs will be tabulated and the rate within the intervention arm estimated.

Adverse Drug Events (ADEs) are also recorded within the intervention arm as three types: a medication error either with or without harm, or an adverse drug reaction. These will be tabulated and a rate estimated both overall and within each ADE category.

6.5 Additional analyses

Two sub-group analyses have been defined for the primary outcome of falls at 6 months. The first will compare the intervention effect between care home types, i.e. nursing versus residential. The second regards the employment status of the PIPs. A subgroup analysis will be carried out comparing the intervention effect between those PIPs that were previously employed, and therefore had an established working relationship, with the study GP practice, and those who were not. In both cases, an interaction term (between treatment and subgrouping factor) will be added to the primary model and formally test for a non-zero value.

Any beneficial effect of the PIP intervention is most likely to be mediated through a decrease in the DBI. A formal secondary analysis (see section 6.2) will estimate the effect of the PIP intervention upon the DBI. To formally test the mediating effect of DBI, the effect of DBI on falls rate will then be estimated using a GEE, adjusting for group membership (this is in order to remove any effect of the PIP intervention on falls mediated via a different causal route). If both models (intervention on DBI and DBI on falls) statistically significant effects then a mediating effect of DBI will be evidenced.

Due to the accidental unblinding of some CHIPPS researchers during the study, an additional baseline analysis will be performed. This will investigate whether there are any differences in baseline characteristics, between those triads where the RAs remained blinded, and those where the RAs were accidently unblinded. An analogous GEE model will again be used for this purpose to estimate subgroup differences in baseline characteristics.

6.6 Software

Analyses will be carried out in SAS (currently version 9.4).

References

1. Alldred DP, Kennedy M-C, Hughes C, Chen T, Miller P Interventions to Optimise prescribing for Older People in Care Homes. Cochrane Database of Systematic Reviews 2016, Issue 2. Art. No.: CD009095. DOI: 10.1002/14651858.CD009095.pub3.
2. Alldred DP, Raynor DK, Hughes C et al. (3 more authors) (2013) Interventions to optimise prescribing for older people in care homes. Cochrane Database of Systematic Reviews, Issue (2). CD009095. ISSN 1469-493X
3. Pan W. (2001) Akaike's Information Criterion in Generalized Estimating Equations. Biometrics,57:120-125.

Appendix : Illustration of Participant (Care Home Residents) Flow .