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Research Methods & Reporting BMJ 2017; 358 doi: (Published 14 July 2017) Cite this as: BMJ 2017;358:j3064 Background: Mental health symptoms among healthcare professionals (HCP) in intensive care units (ICUs) are a significant concern affecting both HCP well-being and patient care outcomes. Cross-sectional studies among members of the European Society of Intensive Care Medicine (ESICM) report up to 50% burnout rates. Determinants of burnout include communication, team cohesion, psychological support, and well-being promotion. We designed the 'Hello Bundle' intervention to mitigate burnout among ICU-HCPs by fostering positive social interactions and a supportive work environment. This justification synthesizes evidence from social psychology, positive psychology, and healthcare communication research to support the intervention. The 'Hello Bundle' aims to enhance interpersonal relationships, improve team cohesion, and reduce burnout rates. The six components include: Hello campaign posters, email reminders, integrating greetings in morning huddles, hello jars, lead-by-example initiatives, and a daily updated hello board in each ICU. This protocol describes a cluster randomized controlled trial to evaluate the effectiveness of the intervention. Methods: This protocol describes a cluster randomized controlled trial (RCT) conducted among ESICM-affiliated ICUs, consisting of at least 73 clusters with in average of 50 respondents per cluster, totaling approximately 7300 participants. Intervention clusters will implement the 6-component Hello Bundle between October 14 and November 10, 2024, while control clusters will be wait-listed to receive the intervention in January 2025 after the RCT concludes. Clusters will be matched based on ICU size (fewer or more than 20 beds), region, and average 2023 mortality. The primary outcome is the proportion of HCPs with burnout between intervention and control clusters at the end of the intervention. Secondary outcomes include comparing the following between clusters: (1) number of HCPs with high emotional exhaustion; (2) number with high depersonalization; (3) number with loss of accomplishment; (4) perception of ethical climate (5) satisfaction at work (VAS); (6) professional conflicts; (7) intention to leave the ICU (VAS); (8) patient-centered care rating; (9) family-centered care rating. The last secondary outcome is the comparison of burnout rates before and after the intervention in the intervention cluster. Outcomes will be based on HCP reports collected within four weeks before and after the intervention. Discussion: This is the first large trial of healthcare communication, social, and positive psychology intervention among ICU-HCPs. It holds the potential to provide valuable insights into effective strategies for addressing burnout in ICU settings, ultimately benefiting both HCPs and patients. Trial registration: This trial was registered on ClinicalTrials.Gov on June 18, 2024. Registration: NCT06453616. Keywords: Burnout; Mental health; Nurses; Psychology; Shortage. Cluster randomized trials (CRTs) differ from individually randomized RCTs in that the unit of randomization is something other than the individual participant or patient. CRTs are in common use in areas such as education and public health research; they are particularly well suited to testing differences in a method or approach to patient care (as opposed to evaluating the physiological effects of a specific intervention).Watch the video module: Understanding Clustering in Cluster Randomized Trials Why Choose Cluster Randomization?There are several reasons why CRT designs might be preferred to or more suitable than a traditional RCT. First, a CRT might be preferred when the target of the intervention is a collective or system rather than a particular person, such as a patient. For example, while a traditional RCT may be better suited to determining whether a novel therapy works in patients with a given disease or condition, a CRT is better able to evaluate whether a new standard of care, guideline recommendation, or other practice-wide, hospital-wide, or system-wide change is affecting patient outcomes. Second, a CRT might be preferred when there is a significant potential for contamination in the study. Contamination occurs when aspects of an intervention are adopted by members of the group that was randomized tonot receive that intervention. (See also "What Is Contamination, and Why Does it Matter?" immediately below).There are also compelling practical reasons for randomizing clusters rather than individuals (Cook et al 2016). For example, in a trial comparing 12-hour nursing shifts to 8-hour shifts, implementing these protocols on a patient-specific level would be nearly impossible. In this case, randomizing wards or floors would be much more practical and would also accommodate the need to avoid contamination.What Is Contamination, and Why Does it Matter?The most compelling reason to randomize at the cluster level rather than at the individual level is the potential for contamination, whereby participants within a cluster are likely to be treated similarly and hence exhibit similar outcomes.When contamination occurs during a clinical trial, it will dilute the observed differences between comparators and can affect the reliability and validity of the study. Example 1: Participants who share the same provider in a trial comparing different weight-loss strategies may meet each other in the waiting room and communicate about their respective strategies, or the provider might not be able to adapt to coaching differently depending on the randomization. Some participants in each group might even adopt elements of both strategies, and neither group would demonstrate the impact of its intended strategy. Randomization at the provider level, with each provider coaching only one of the strategies, would reduce the risk of contamination.Example 2: A trial evaluating a campaign designed to reduce nosocomial infections by encouraging better staff handwashing practices might include posters in each of the rooms. Staff generally cover several rooms on a floor and would be exposed to the posters, which would likely change their behavior if the posters were actually effective. Not only would it be infeasible to randomize at the provider or patient level, doing so would minimize the difference between groups due to the contamination. The campaign might then be declared unsuccessful despite actually having had a positive effect. The solution would be to randomize different areas of the hospital (taking care to consider potential confounding as described in the coming sections) with only half of the areas receiving the posters. Although avoidance of contamination is one of the most important reasons for using CRT designs, pragmatic concerns can dominate the need for cluster randomization when it is practically impossible to randomize at an individual level.Previous Section Next Section Cook AJ, Delong E, Murray DM, Vollmer WM, Heagerty PJ. 2016. Statistical lessons learned for designing cluster randomized pragmatic clinical trials from the NIH Health Care Systems Collaboratory Biostatistics and Design Core. Clin Trials. 13:504-512. doi:10.1177/1740774516646578. PMID: 27179253. January 22, 2021: Added embedded video (change made by G. Uhlenbrauck).July 2, 2020: Minor corrections to layout and formatting (changes made by D. Seils).May 27, 2020: Added Heagerty to the contributors list and reordered the sections of this chapter as part the annual content update (changed made by D. Seils).January 16, 2019: Added a resource to the Resources box and made nonsubstantive changes to the text as part of the annual content update (changes made by D. Seils).Published August 25, 2017 Welcome to the Living Textbook of pragmatic clinical trials, a collection of knowledge from the NIH Pragmatic Trials Collaboratory. Pragmatic clinical trials present an opportunity to efficiently generate high-quality evidence to inform medical decision-making. However, these trials pose different challenges than traditional clinical trials. The Living Textbook reflects a collection of special considerations and best practices in the design, conduct, and reporting of pragmatic clinical trials. NIH Collaboratory Pragmatic clinical trials that address questions of major public health importance and provide proof of concept forinnovative pragmatic research designs.CORESWorking groups that support the conductof NIH Collaboratory Trials and generate guidance addressing implementation challenges.DISTRIBUTED RESEARCH NETWORKNetwork enablinginvestigators to collaborate in the use of electronic health data while safeguarding protectedhealth information. June 6 @ 1:00 pm - 2:00 pmJune 13 @ 1:00 pm - 2:00 pmJune 20 @ 1:00 pm - 2:00 pmJune 27 @ 1:00 pm - 2:00 pmView Calendar May 30, 2025: Randomizing in Clinical Care in the KP-VACCINATE Megatrial, in This Weeks PCT Grand RoundsIn this Fridays Rethinking Clinical Trials Grand Rounds, Ankeet Bhatt of the Kaiser Permanente Northern California Division of Research will present Embedding Randomization Into Clinical Care in Learning Healthcare Systems: ...May 28, 2025: New NIH Collaboratory Learning Module Explores Challenges and Possibilities of Working With Electronic Health Record DataThe NIH Pragmatic Trials Collaboratory has launched a new learning module, Healthcare Data Interoperability and Standardization for Research, exploring the complexities of collecting, storing, and transforming healthcare data in the ...May 19, 2025: Latest Podcast Episode Features the Results of ACP PEACEIn a new episode of our Rethinking Clinical Trials Podcast, Drs. Angelo Volandes and James Tulsky speak with host Dr. Adrian Hernandez about the results of the ACP PEACE study.Listen ...More News Promoting PRAGMATIC RESEARCH to increase the availability of high-quality medical evidence and IMPROVE patient care. Share copy and redistribute the material in any medium or format for any purpose, even commercially. Adapt remix, transform, and build upon the material for any purpose, even commercially. The licensor cannot revoke these freedoms as long as you follow the license terms. Attribution You must give appropriate credit , provide a link to the license, and indicate if changes were made . You may do so in any reasonable manner, but not in any way that suggests the licensor endorses you or your use. ShareAlike If you remix, transform, or build upon the material, you must distribute your contributions under the same license as the original. No additional restrictions You may not apply legal terms or technological measures that legally restrict others from doing anything the license permits. You do not have to comply with the license for elements of the material in the public domain or where your use is permitted by an applicable exception or limitation . No warranties are given. The license may not give you all of the permissions necessary for your intended use. For example, other rights such as publicity, privacy, or moral rights may limit how you use the material. This is a cluster RCT conducted in primary care involving participating GP-PIP-care home triads in four study locations linked geographically to the Universities of East Anglia, Leeds, Aberdeen and Queens Belfast, (hereafter referred to by the University identity). A complete list of study sites is available from the Senior Programme Coordinator Mrs. Laura Watts; L.Watts1@uea.ac.uk.The objectives for the cluster RCT are:To use an embedded (internal) pilot study to confirm: the feasibility of recruiting sufficient GP practices, PIPs, care homes and residents the availability of data for primary outcome at 3months that there are no intervention-related safety concernsIf the pilot is successful, to deliver a full RCT to:Describe the clinical effectiveness of the intervention: PIPs assuming responsibility for medicines management of elderly residents in care homesTo estimate the cost-effectiveness of the interventionThe interventionThe intervention will be delivered by trained PIPs for a period of 6 months. The training programme comprises 2 days of face-to-face instruction, time in practice to develop relationships with the GP and care home staff, and to address any self-assessed competency gaps supported by a mentor, and a formal final sign-off by a GP, who is independent of the research. The development and evaluation of the training programme will be published separately.The intervention has been tested in a feasibility study [18]. It involves the PIP, in collaboration with the care home residents GP, assuming responsibility for managing the medicines of the resident, including:Reviewing residents medication and developing and implementing a pharmaceutical care planAssuming prescribing responsibilitiesSupporting systematic ordering, prescribing and administration processes with each care home, GP practice and supplying pharmacy where neededProviding training in care home and GP practiceCommunicating with GP practice, care home, supplying community pharmacy and study teamDetails of the intervention to be delivered by the PIP are in the CHIPPS Service Specification (Additionalfile1) which was developed in previous work packages.The study PIPs will work closely with the care home staff and the residents GP, and communicate regularly with both parties. Once residents are recruited, the local researcher will maintain regular contact with the PIP to ensure adherence to study procedures. During the study there will be a check of a random 20% sample of the pharmaceutical care plans and associated resident documents by a study geriatrician, to ensure clinical appropriateness and safety. Additionally, should any problem arise, the geriatrician will discuss this with the Programme (DW, RH) or Trial (CB, RH) Chief Investigator or local Principal Investigator (DA,CB, CH, DW). At the end of the study period the intervention will cease unless the GP practice and care home mutually agree to continue to deliver it outwith the framework of the research programme.The comparator will be usual GP-led care. Whilst pharmacists may already be providing some services for care homes, these are usually annual or biannual visits and unlike the intensive approach proposed here. At the end of the study period all PIPs in the control practices will be offered access to the study training. Any medical practices which employ pharmacists to provide services to care homes of similar intensity to that which we propose will be excluded.Study participantsThe inclusion and exclusion criteria for the study participants are:The PIP Inclusion criteria: Registered as a PIP with regulating body (GPhC (England and Scotland) or Pharmaceutical Society of Northern Ireland (Northern Ireland)) Following CHIPPS study training, can demonstrate to their mentor and independent GP assessor competence to deliver the service specification Ability to work flexibly and commit a minimum of 16h a month to deliver the service for 6 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-focussed services GP practice Inclusion criteria: The GP practice must manage sufficient care home residents to support recruitment of the target of approximately 20 eligible participants1 Exclusion criteria: noneCare 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 aged over 65 years Primarily caring for residents aged over 65years 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 other intensive medication-focussed services Care homes which receive regular (e.g. a monthly visit or more frequently), from another healthcare professional, providing other intensive medication-focussed services Care homes which are currently under formal investigation with the 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.) Care home residents Inclusion criteria: Under the care of the participating GP practice Aged 65years or over Currently prescribed at least one regular medication They or their appropriate representative is/are able to provide informed consent/assent2 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) [19] Have additional limitations on their residence (e.g. held securely) Participating in another intervention research study Study outcomesThe study outcomes and data sources are summarised below. Primary outcome Fall rate per person at 6months as documented in the care home falls record Secondary outcomes Proxy resident EQ-5D-5L (quality of life) at baseline, 3months and 6months[20] Face-to-face self-reported resident EQ-5D-5L (for participants with capacity) at baseline, 3months and 6months [20] Proxy Barthel Index (physical functioning) completed at baseline, and 6months by identified member of care home staff [21] Fall rate per person in the past 3 months at baseline, 3 months and6 months as documented in care home records Health-service utilisation (and associated costs) in the past 3 months at baseline and in the past 6months at 6months follow-up, collected from care home and GP records Mortality Change in hospitalisation rate per person (baseline rate defined as 3months prior to randomisation compared with hospitalisation rate at 6-month follow-up) collected from care home records Drug Burden Index (DBI) [22] at baseline and 6months with medication data collected from GP records Cost-effectiveness of the PIP intervention from the perspective of the NHS and care home In addition, in the internal pilot stage which is now completed, the following data (stop-go criteria) were collected.Quantification of interest from medical practices-PIPs-care home(s) to confirm the viability of planned target recruitment numbers and time line>30% of eligible patients have been recruited (from those invited in each home)>80% of data are available at 3months for falls dataNo significant intervention-related safety concernsA detailed process evaluation is being conducted following MRC guidance [23] and will be published separately.Participant identification and recruitmentRecruitment and consent will be complex due to the need to identify medical practices with a PIP, recruit homes and then residents for each triad. Initially, PIPs and GPs will be recruited concurrently, with the care homes recruited subsequently, followed by the residents. Copies of recruitment documentation to be used in England and Northern Ireland are attached in Additionalfile2. Scottish versions required some slight changes in terminology, to accommodate the different regulations for adults with incapacity, and are available on request.PIP and GP recruitmentEligible PIPs in each area will be identified using local networks, and initial informal contact will be followed by formal invitation to PIP and GP practice (letter of invitation, Participant Information Sheet, Consent Form) and consent. PIPs will be recruited, together with the GP practice with whom they should ideally have an already established close working relationship. Basic demographic information about interested GP practices and their linked care home (e.g. the resident mix, home ownership) will be collected to allow purposive sampling if numbers allow. However, if this does not provide sufficient GP practice-PIP pairings, PIPs and GP practices will be approached separately and linked before care homes are approached.Care home recruitmentThe participating GP practice will approach one (or more, if necessary) of their eligible care homes and invite them to take part in the study. If the care home manager expresses interest, they will be sent a formal invitation pack by the local researcher (including a letter and Information Sheet). If a care home declines participation, the GP will contact another home and invite them to participate. If there are insufficient residents in one home, then up to two further homes can be recruited. Where a home does not wish to participate, and there is no alternative home, a different GP practice in that area will be identified and recruited and the process to recruit the care home(s) will be repeated.Resident recruitmentGPs will identify from their lists of registered patients, those resident in the participating care homes taking one or more medications, and screen them against the study inclusion and exclusion criteria. Reasons for any exclusions will be recorded on a standard form collected by the local researcher. Care home managers will hand out invitation packs (invitation letter from GP, Participant Information Sheet (spoken version if necessary) and consent form) directly to potential resident participants. The care home manager will visit each resident after at least 24h, and obtain verbal consent for the local researcher to be allowed to approach them to discuss participation in the study. For residents who are considered by the manager to lack capacity, packs will be posted to the residents next of kin. To minimise selection bias, packs will be distributed in the order of the list of names from the GP.The local researcher will meet with interested residents, administer the Capacity Assessment for Residents Form (see Additionalfile3) and, if appropriate, take fully informed consent. For those without capacity, there are country-specific regulations to adhere to for each of the home nations; these are detailed in Table1. The approach is in line with recommended practice [27].Table 1 Obtaining third-party consent for residents without capacity in the three devolved home countriesIf someone loses capacity during the 6 months of the study, they will remain in the study. This is a specific statement on the Consent Form: I agree to continue participating in the study if I lose capacity before the end of the study. If someone should lose capacity during the study, continued participation will be confirmed with the next of kin following the same procedures as for initial consent.At each follow up visit, the care home manager will be asked if any participants have re-gained capacity. Should anyone re-gain capacity during the course of the study, and if the resident is willing, their personal consent to continue will be obtained using the template Resident Recovered Capacity documents, and in England it would be with the original Patient Information and Consent. It is made clear in the Participant Information Sheets that if residents decide not to continue, all the information collected so far will remain in the study, but no further information will be collected.The recruitment flow chart and participant time line are shown in Figs 1 and 2 below.Fig. 1Fig. 2Randomisation will be at practice level rather than the home level in order to minimise contamination which may occur if two homes were in the same practice and one received the intervention whilst the other did not. It is not appropriate to randomise at resident level as the intervention is designed to affect medication-related processes at an institutional (care home), as well as a resident, level and, therefore, control participants would not be immune to its effects.Blocked randomisation will be undertaken by geographical area, using a web-based electronic randomisation system integrated into the study database. The triads will be informed of their randomisation group by the Senior Programme Coordinator. Local Principal investigators at each geographical site will be informed of the allocations of their triads, (CB, DW, DA, CH) and one of the trial co-CIs (CB) will be informed of all allocations by coded emails. The GP and care homes in each triad are blinded until the care home residents have been recruited. The PIPs are unblinded once randomisation has been completed as the intervention PIPs have to complete training and competency assessment prior to the intervention start. Due to the nature of the intervention, study participants cannot be blinded to the intervention. The local researchers will be blinded until after care home residents have been recruited and baseline data collection has been completed. Should they inadvertently be unblinded they are asked to inform the Senior Programme Coordinator. As the researcher may or may not be correct in suspecting that they know the group allocation their perceived unblinding is not confirmed by the Senior Programme Coordinator until after baseline data have been collected. The potential unblinding is noted on the non-conformance report which is reviewed by the PSC and DMC. The trial statistician is advised of the triads where there is potential unblinding and will assess whether this appears to have resulted in any bias in reporting by comparison with triads where there was no reported unblinding.Data collectionData, as specified earlier, will be collected, by the local researcher, from GP practice and care home paper and/or digital records. Data will be coded and entered into either paper Case Record Forms (CRFs) or electronically using tablets. Data entered on paper records will be subsequently entered into a centrally held Norwich Clinical Trials Unit (NCTU) CHIPPS REDCap [28] database by local researchers. Data collected electronically will be entered into the REDCap database at the time of data collection if there is Internet connectivity, or if working off-line, at the next time the device is synchronised. Data will be protected using established NCTU procedures.Data managementData management is detailed in the Data Management Plan version 1: 21 November.2017. Local research staff will receive training in all aspects of data collection and management. Identification logs, screening logs and enrolment logs will be kept at each of the four University locations in a locked cabinet within a secured room. All data will be handled in accordance with the General Data Protection Regulations 2018. All participants (GPs, care homes and residents) will be given a unique study Participant Identification Number (PIN). Data will be entered under this identification number onto the centrally held database stored on the servers based at NCTU. Access to the database will be controlled with unique usernames and encrypted passwords, and restricted to members of the CHIPPS study team, and external regulators if requested. The servers are protected by firewalls and maintained according to best practice. The physical location of the servers is protected by CCTV and security door access.The database and associated code lists have been developed by the Study Coordinators in conjunction with NCTU. The database software (REDCap) provides a number of features to help maintain data quality, including: maintaining an audit trail, allowing custom validations on all data, allowing users to raise data-query requests, and search facilities to identify validation failure/missing data.Once data entry is complete the database will be locked prior to any trial analysis or unblinding. The Data Management Team will provide a read-only link for the Trial Statistician to access the data. After completion of the study the database will be retained on the servers of NCTU for on-going analysis, for 10years.The screening and enrolment logs will remain at the care home. For recruitment monitoring purposes, identifiable patient information will be redacted, and pseudoanonymised copies of these logs being taken to the research office. Following consent, identifiable (consented participants only) screening data, linked to the Participant Identification Number, will be held locally at the University research office, in a locked filing cabinet. After completion of the study the identification, screening and enrolment logs will be securely archived at each University research office for 10years, unless otherwise advised by NCTU.Sample sizeA sample size of 880 (440 in each arm) would detect a decrease in fall rate from 1.50 per individual over 6months to 1.178 with 80% statistical power. These assumptions are based upon data from the CAREMED [29] study, which found a fall rate of 1.5 per individual over a 6-month period and an intraclass correlation coefficient (ICC) no greater than 0.07 for the endpoint of interest. 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 [30]. The CAREMED trial indicated a mortality rate of 33% and further loss to follow-up of 5% over 12months. Thus, a reasonable estimate of total losses due to mortality or other reasons over 6 months would be 20%, and is taken into account in the above. However, we will use data, where possible, up to the point at which someone withdraws from the study.To recruit 880 resident participants there will be a recruitment target of 44 triads, with a mean of 20 participants from each, a loss rate of no more than 20% and an ICC of 0.05.Statistical methodsAn intention-to-treat analysis will be conducted. The primary outcome (falls per resident) will mostly 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, prognostic variables (specified prior to analysis) and group as a fixed factor. 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. The Poisson assumption will be assessed with fit statistics and, if appropriate, a Zero Inflated Poisson, or a Poisson model with an over-dispersion term will be considered. An analogue GEE model will be used for secondary outcomes, with an appropriate change to the error distribution (e.g. Normal). The estimate of the between-group difference will be provided with a 95% confidence interval and tested at the 5% significance level.There are currently no plans for any subgroup analyses.Safety reporting of Serious Adverse EventsThe processes for the recording of SUSARs (Sudden Unexpected Serious Adverse Events), SAEs (Serious Adverse Events) and AEs (Adverse Events) and near misses in PIP documentation, GP and care home records, notification to NCTU, CI review, expedited and periodic reporting to REC will be documented in the study-specific Safety Management Plan.For the purposes of this trial, SAEs are defined as inpatient hospitalisation and death. The expedited, i.e. immediate reporting is required if they are:related to the study (i.e. they resulted from the intervention) andunexpected (referred to hereafter as SUSARs)A mixture of prospective and retrospective SUSAR notification will be used.Prospective: from the beginning of the intervention until 30days after the intervention ends GPs will be asked to report SUSARs immediately via a SUSAR Form to a dedicated NCTU safety email address.Retrospective: a systematic retrospective collection of SAEs will be conducted in both intervention and control practices, whereby the NCTU Trial Manager will contact every participating care home once a month and ask about any SAEs. Deaths and hospitalisations in both arms will also be reported to the REC via the annual report.The causality assessment of the SAE should be given by the GP. If the GP identifies a positive causality (i.e. the SAE is linked to the PIP intervention and is, therefore, a SUSAR) then this is signed off by the CI. The GP must assess the causality of all SAEs in relation to the PIP intervention using the definitions in the table below. If the event is classified as serious and assessed as being related to the PIP intervention then a SUSAR Form must be completed and NCTU notified within 24h.All staff involved in the care of study participants (i.e. PIPs, care home staff, any other healthcare professionals) will also be asked to report, immediately, to a separate dedicated email address (chipps.safety@uea.ac.uk), any events about which they are concerned. NCTU can be notified of any further safety concerns or near misses by all staff involved in the care of study participants via a study-specific safety email address Table2.Table 2 Serious Adverse Event (SAE) causality definitionsThe trial is overseen by a Trial Management Group (TMG) comprising the Programme Chief Investigator, The Trial Co-Chief Investigators, the local Principal Investigators, the Senior Programme Manager, the NCTU Manager and the Programme Administrator. The trial is advised by a Programme Steering Committee (PSC) which provides expert oversight of the trial, making decisions as to the future continuation (or otherwise) of the trial, by monitoring recruitment rates, approving proposals by the TMG concerning any change to the design of the trial, as well as receiving letters of feedback from the independent Data Monitoring Committee (DMC). The DMC comprises a statistician, an academic pharmacist with an interest in patient safety, and an academic GP (Chair) with extensive trials experience. The DMC has a remit to monitor the safety of the trial participants through examination of trial safety and efficacy data, thereby providing advice to the Chair of the Programme Steering Committee (PSC). The DMC Chair informs the Chair of the PSC if, in the view of the DMC, one trial arm is clearly indicated or contraindicated (for all participants or a particular category of participants), and there is a reasonable expectation that this new evidence would materially influence patient management.There is a study Quality Management and Monitoring Plan (version 2: 1 June.2018) which details the procedures for quality control and data monitoring by the NCTU. The study will also be subject to random monitoring by the host Universities and local Research and Development Departments. This is a cluster RCT conducted in primary care involving participating GP-PIP-care home triads in four study locations linked geographically to the Universities of East Anglia, Leeds, Aberdeen and Queens Belfast, (hereafter referred to by the University identity). A complete list of study sites is available from the Senior Programme Coordinator Mrs. Laura Watts; L.Watts1@uea.ac.uk.The objectives for the cluster RCT are:To use an embedded (internal) pilot study to confirm: the feasibility of recruiting sufficient GP practices, PIPs, care homes and residents the availability of data for primary outcome at 3months that there are no intervention-related safety concernsIf the pilot is successful, to deliver a full RCT to:Describe the clinical effectiveness of the intervention: PIPs assuming responsibility for medicines management of elderly residents in care homesTo estimate the cost-effectiveness of the interventionThe interventionThe intervention will be delivered by trained PIPs for a period of 6 months. The training programme comprises 2 days of face-to-face instruction, time in practice to develop relationships with the GP and care home staff, and to address any self-assessed competency gaps supported by a mentor, and a formal final sign-off by a GP, who is independent of the research. The development and evaluation of the training programme will be published separately.The intervention has been tested in a feasibility study [18]. It involves the PIP, in collaboration with the care home residents GP, assuming responsibility for managing the medicines of the resident, including:Reviewing residents medication and developing and implementing a pharmaceutical care planAssuming prescribing responsibilitiesSupporting systematic ordering, prescribing and administration processes with each care home, GP practice and supplying pharmacy where neededProviding training in care home and GP practiceCommunicating with GP practice, care home, supplying community pharmacy and study teamDetails of the intervention to be delivered by the PIP are in the CHIPPS Service Specification (Additionalfile1) which was developed in previous work packages.The study PIPs will work closely with the care home staff and the residents GP, and communicate regularly with both parties. Once residents are recruited, the local researcher will maintain regular contact with the PIP to ensure adherence to study procedures. During the study there will be a check of a random 20% sample of the pharmaceutical care plans and associated resident documents by a study geriatrician, to ensure clinical appropriateness and safety. Additionally, should any problem arise, the geriatrician will discuss this with the Programme (DW, RH) or Trial (CB, RH) Chief Investigator or local Principal Investigator (DA,CB, CH, DW). At the end of the study period the intervention will cease unless the GP practice and care home mutually agree to continue to deliver it outwith the framework of the research programme.The comparator will be usual GP-led care. Whilst pharmacists may already be providing some services for care homes, these are usually annual or biannual visits and unlike the intensive approach proposed here. At the end of the study period all PIPs in the control practices will be offered access to the study training. Any medical practices which employ pharmacists to provide services to care homes of similar intensity to that which we propose will be excluded.Study participantsThe inclusion and exclusion criteria for the study participants are:The PIP Inclusion criteria: Registered as a PIP with regulating body (GPhC (England and Scotland) or Pharmaceutical Society of Northern Ireland (Northern Ireland)) Following CHIPPS study training, can demonstrate to their mentor and independent GP assessor competence to deliver the service specification Ability to work flexibly and commit a minimum of 16h a month to deliver the service for 6 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-focussed services GP practice Inclusion criteria: The GP practice must manage sufficient care home residents to support recruitment of the target of approximately 20 eligible participants1 Exclusion criteria: noneCare 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 aged over 65 years Primarily caring for residents aged over 65years 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 other intensive medication-focussed services Care homes which receive regular (e.g. a monthly visit or more frequently), from another healthcare professional, providing other intensive medication-focussed services Care homes which are currently under formal investigation with the 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.) Care home residents Inclusion criteria: Under the care of the participating GP practice Aged 65years or over Currently prescribed at least one regular medication They or their appropriate representative is/are able to provide informed consent/assent2 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) [19] Have additional limitations on their residence (e.g. held securely) Participating in another intervention research study Study outcomesThe study outcomes and data sources are summarised below. 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Initially, PIPs and GPs will be recruited concurrently, with the care homes recruited subsequently, followed by the residents. Copies of recruitment documentation to be used in England and Northern Ireland are attached in Additionalfile2. Scottish versions required some slight changes in terminology, to accommodate the different regulations for adults with incapacity, and are available on request.PIP and GP recruitmentEligible PIPs in each area will be identified using local networks, and initial informal contact will be followed by formal invitation to PIP and GP practice (letter of invitation, Participant Information Sheet, Consent Form) and consent. PIPs will be recruited, together with the GP practice with whom they should ideally have an already established close working relationship. Basic demographic information about interested GP practices and their linked care home (e.g. the resident mix, home ownership) will be collected to allow purposive sampling if numbers allow. 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Where a home does not wish to participate, and there is no alternative home, a different GP practice in that area will be identified and recruited and the process to recruit the care home(s) will be repeated.Resident recruitmentGPs will identify from their lists of registered patients, those resident in the participating care homes taking one or more medications, and screen them against the study inclusion and exclusion criteria. Reasons for any exclusions will be recorded on a standard form collected by the local researcher. Care home managers will hand out invitation packs (invitation letter from GP, Participant Information Sheet (spoken version if necessary) and consent form) directly to potential resident participants. The care home manager will visit each resident after at least 24h, and obtain verbal consent for the local researcher to be allowed to approach them to discuss participation in the study. 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If someone should lose capacity during the study, continued participation will be confirmed with the next of kin following the same procedures as for initial consent.At each follow up visit, the care home manager will be asked if any participants have re-gained capacity. Should anyone re-gain capacity during the course of the study, and if the resident is willing, their personal consent to continue will be obtained using the template Resident Recovered Capacity documents, and in England it would be with the original Patient Information and Consent. 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The triads will be informed of their randomisation group by the Senior Programme Coordinator. Local Principal investigators at each geographical site will be informed of the allocations of their triads, (CB, DW, DA, CH) and one of the trial co-CIs (CB) will be informed of all allocations by coded emails. The GP and care homes in each triad are blinded until the care home residents have been recruited. The PIPs are unblinded once randomisation has been completed as the intervention PIPs have to complete training and competency assessment prior to the intervention start. Due to the nature of the intervention, study participants cannot be blinded to the intervention. The local researchers will be blinded until after care home residents have been recruited and baseline data collection has been completed. Should they inadvertently be unblinded they are asked to inform the Senior Programme Coordinator. As the researcher may or may not be correct in suspecting that they know the group allocation their perceived unblinding is not confirmed by the Senior Programme Coordinator until after baseline data have been collected. The potential unblinding is noted on the non-conformance report which is reviewed by the PSC and DMC. The trial statistician is advised of the triads where there is potential unblinding and will assess whether this appears to have resulted in any bias in reporting by comparison with triads where there was no reported unblinding.Data collectionData, as specified earlier, will be collected, by the local researcher, from GP practice and care home paper and/or digital records. Data will be coded and entered into either paper Case Record Forms (CRFs) or electronically using tablets. Data entered on paper records will be subsequently entered into a centrally held Norwich Clinical Trials Unit (NCTU) CHIPPS REDCap [28] database by local researchers. Data collected electronically will be entered into the REDCap database at the time of data collection if there is Internet connectivity, or if working off-line, at the next time the device is synchronised. Data will be protected using established NCTU procedures.Data managementData management is detailed in the Data Management Plan version 1: 21 November.2017. Local research staff will receive training in all aspects of data collection and management. Identification logs, screening logs and enrolment logs will be kept at each of the four University locations in a locked cabinet within a secured room. All data will be handled in accordance with the General Data Protection Regulations 2018. All participants (GPs, care homes and residents) will be given a unique study Participant Identification Number (PIN). Data will be entered under this identification number onto the centrally held database stored on the servers based at NCTU. Access to the database will be controlled with unique usernames and encrypted passwords, and restricted to members of the CHIPPS study team, and external regulators if requested. The servers are protected by firewalls and maintained according to best practice. The physical location of the servers is protected by CCTV and security door access.The database and associated code lists have been developed by the Study Coordinators in conjunction with NCTU. The database software (REDCap) provides a number of features to help maintain data quality, including: maintaining an audit trail, allowing custom validations on all data, allowing users to raise data-query requests, and search facilities to identify validation failure/missing data.Once data entry is complete the database will be locked prior to any trial analysis or unblinding. The Data Management Team will provide a read-only link for the Trial Statistician to access the data. 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These assumptions are based upon data from the CAREMED [29] study, which found a fall rate of 1.5 per individual over a 6-month period and an intraclass correlation coefficient (ICC) no greater than 0.07 for the endpoint of interest. 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 [30]. The CAREMED trial indicated a mortality rate of 33% and further loss to follow-up of 5% over 12months. Thus, a reasonable estimate of total losses due to mortality or other reasons over 6 months would be 20%, and is taken into account in the above. However, we will use data, where possible, up to the point at which someone withdraws from the study.To recruit 880 resident participants there will be a recruitment target of 44 triads, with a mean of 20 participants from each, a loss rate of no more than 20% and an ICC of 0.05.Statistical methodsAn intention-to-treat analysis will be conducted. The primary outcome (falls per resident) will mostly 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, prognostic variables (specified prior to analysis) and group as a fixed factor. 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. The Poisson assumption will be assessed with fit statistics and, if appropriate, a Zero Inflated Poisson, or a Poisson model with an over-dispersion term will be considered. An analogue GEE model will be used for secondary outcomes, with an appropriate change to the error distribution (e.g. Normal). The estimate of the between-group difference will be provided with a 95% confidence interval and tested at the 5% significance level.There are currently no plans for any subgroup analyses.Safety reporting of Serious Adverse EventsThe processes for the recording of SUSARs (Sudden Unexpected Serious Adverse Events), SAEs (Serious Adverse Events) and AEs (Adverse Events) and near misses in PIP documentation, GP and care home records, notification to NCTU, CI review, expedited and periodic reporting to REC will be documented in the study-specific Safety Management Plan.For the purposes of this trial, SAEs are defined as inpatient hospitalisation and death. The expedited, i.e. immediate reporting is required if they are:related to the study (i.e. they resulted from the intervention) andunexpected (referred to hereafter as SUSARs)A mixture of prospective and retrospective SUSAR notification will be used.Prospective: from the beginning of the intervention until 30days after the intervention ends GPs will be asked to report SUSARs immediately via a SUSAR Form to a dedicated NCTU safety email address.Retrospective: a systematic retrospective collection of SAEs will be conducted in both intervention and control practices, whereby the NCTU Trial Manager will contact every participating care home once a month and ask about any SAEs. Deaths and hospitalisations in both arms will also be reported to the REC via the annual report.The causality assessment of the SAE should be given by the GP. If the GP identifies a positive causality (i.e. the SAE is linked to the PIP intervention and is, therefore, a SUSAR) then this is signed off by the CI. The GP must assess the causality of all SAEs in relation to the PIP intervention using the definitions in the table below. If the event is classified as serious and assessed as being related to the PIP intervention then a SUSAR Form must be completed and NCTU notified within 24h.All staff involved in the care of study participants (i.e. PIPs, care home staff, any other healthcare professionals) will also be asked to report, immediately, to a separate dedicated email address (chipps.safety@uea.ac.uk), any events about which they are concerned. NCTU can be notified of any further safety concerns or near misses by all staff involved in the care of study participants via a study-specific safety email address Table2.Table 2 Serious Adverse Event (SAE) causality definitionsThe trial is overseen by a Trial Management Group (TMG) comprising the Programme Chief Investigator, The Trial Co-Chief Investigators, the local Principal Investigators, the Senior Programme Manager, the NCTU Manager and the Programme Administrator. The trial is advised by a Programme Steering Committee (PSC) which provides expert oversight of the trial, making decisions as to the future continuation (or otherwise) of the trial, by monitoring recruitment rates, approving proposals by the TMG concerning any change to the design of the trial, as well as receiving letters of feedback from the independent Data Monitoring Committee (DMC). The DMC comprises a statistician, an academic pharmacist with an interest in patient safety, and an academic GP (Chair) with extensive trials experience. The DMC has a remit to monitor the safety of the trial participants through examination of trial safety and efficacy data, thereby providing advice to the Chair of the Programme Steering Committee (PSC). The DMC Chair informs the Chair of the PSC if, in the view of the DMC, one trial arm is clearly indicated or contraindicated (for all participants or a particular category of participants), and there is a reasonable expectation that this new evidence would materially influence patient management.There is a study Quality Management and Monitoring Plan (version 2: 1 June.2018) which details the procedures for quality control and data monitoring by the NCTU. The study will also be subject to random monitoring by the host Universities and local Research and Development Departments.This is a cluster RCT conducted in primary care involving participating GP-PIP-care home triads in four study locations

linked geographically to the Universities of East Anglia, Leeds, Aberdeen and Queens Belfast, (hereafter referred to by the University identity). A complete list of study sites is available from the Senior Programme Coordinator Mrs. Laura Watts; L.Watts1@uea.ac.uk.The objectives for the cluster RCT are:To use an embedded (internal) pilot study to confirm: the feasibility of recruiting sufficient GP practices, PIPs, care homes and residents the availability of data for primary outcome at 3months that there are no intervention-related safety concernsIf the pilot is successful, to deliver a full RCT to:Describe the clinical effectiveness of the intervention: PIPs assuming responsibility for medicines management of elderly residents in care homesTo estimate the cost-effectiveness of the interventionThe interventionThe intervention will be delivered by trained PIPs for a period of 6 months. The training programme comprises 2 days of face-to-face instruction, time in practice to develop relationships with the GP and care home staff, and to address any self-assessed competency gaps supported by a mentor, and a formal final sign-off by a GP, who is independent of the research. The development and evaluation of the training programme will be published separately.The intervention has been tested in a feasibility study [18]. It involves the PIP, in collaboration with the care home residents GP, assuming responsibility for managing the medicines of the resident, including:Reviewing residents medication and developing and implementing a pharmaceutical care planAssuming prescribing responsibilitiesSupporting systematic ordering, prescribing and administration processes with each care home, GP practice and supplying pharmacy where neededProviding training in care home and GP practiceCommunicating with GP practice, care home, supplying community pharmacy and study teamDetails of the intervention to be delivered by the PIP are in the CHIPPS Service Specification (Additionalfile1) which was developed in previous work packages.The study PIPs will work closely with the care home staff and the residents GP, and communicate regularly with both parties. Once residents are recruited, the local researcher will maintain regular contact with the PIP to ensure adherence to study procedures. During the study there will be a check of a random 20% sample of the pharmaceutical care plans and associated resident documents by a study geriatrician, to ensure clinical appropriateness and safety. Additionally, should any problem arise, the geriatrician will discuss this with the Programme (DW, RH) or Trial (CB, RH) Chief Investigator or local Principal Investigator (DA,CB, CH, DW). At the end of the study period the intervention will cease unless the GP practice and care home mutually agree to continue to deliver it outwith the framework of the research programme.The comparator will be usual GP-led care. Whilst pharmacists may already be providing some services for care homes, these are usually annual or biannual visits and unlike the intensive approach proposed here. At the end of the study period all PIPs in the control practices will be offered access to the study training. 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These assumptions are based upon data from the CAREMED [29] study, which found a fall rate of 1.5 per individual over a 6-month period and an intraclass correlation coefficient (ICC) no greater than 0.07 for the endpoint of interest. 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 [30]. The CAREMED trial indicated a mortality rate of 33% and further loss to follow-up of 5% over 12months. Thus, a reasonable estimate of total losses due to mortality or other reasons over 6 months would be 20%, and is taken into account in the above. However, we will use data, where possible, up to the point at which someone withdraws from the study.To recruit 880 resident participants there will be a recruitment target of 44 triads, with a mean of 20 participants from each, a loss rate of no more than 20% and an ICC of 0.05.Statistical methodsAn intention-to-treat analysis will be conducted. The primary outcome (falls per resident) will mostly 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, prognostic variables (specified prior to analysis) and group as a fixed factor. 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. The Poisson assumption will be assessed with fit statistics and, if appropriate, a Zero Inflated Poisson, or a Poisson model with an over-dispersion term will be considered. An analogue GEE model will be used for secondary outcomes, with an appropriate change to the error distribution (e.g. Normal). The estimate of the between-group difference will be provided with a 95% confidence interval and tested at the 5% significance level.There are currently no plans for any subgroup analyses.Safety reporting of Serious Adverse EventsThe processes for the recording of SUSARs (Sudden Unexpected Serious Adverse Events), SAEs (Serious Adverse Events) and AEs (Adverse Events) and near misses in PIP documentation, GP and care home records, notification to NCTU, CI review, expedited and periodic reporting to REC will be documented in the study-specific Safety Management Plan.For the purposes of this trial, SAEs are defined as inpatient hospitalisation and death. The expedited, i.e. immediate reporting is required if they are:related to the study (i.e. they resulted from the intervention) andunexpected (referred to hereafter as SUSARs)A mixture of prospective and retrospective SUSAR notification will be used.Prospective: from the beginning of the intervention until 30days after the intervention ends GPs will be asked to report SUSARs immediately via a SUSAR Form to a dedicated NCTU safety email address.Retrospective: a systematic retrospective collection of SAEs will be conducted in both intervention and control practices, whereby the NCTU Trial Manager will contact every participating care home once a month and ask about any SAEs. Deaths and hospitalisations in both arms will also be reported to the REC via the annual report.The causality assessment of the SAE should be given by the GP. If the GP identifies a positive causality (i.e. the SAE is linked to the PIP intervention and is, therefore, a SUSAR) then this is signed off by the CI. The GP must assess the causality of all SAEs in relation to the PIP intervention using the definitions in the table below. If the event is classified as serious and assessed as being related to the PIP intervention then a SUSAR Form must be completed and NCTU notified within 24h.All staff involved in the care of study participants (i.e. PIPs, care home staff, any other healthcare professionals) will also be asked to report, immediately, to a separate dedicated email address (chipps.safety@uea.ac.uk), any events about which they are concerned. NCTU can be notified of any further safety concerns or near misses by all staff involved in the care of study participants via a study-specific safety email address Table2.Table 2 Serious Adverse Event (SAE) causality definitionsThe trial is overseen by a Trial Management Group (TMG) comprising the Programme Chief Investigator, The Trial Co-Chief Investigators, the local Principal Investigators, the Senior Programme Manager, the NCTU Manager and the Programme Administrator. The trial is advised by a Programme Steering Committee (PSC) which provides expert oversight of the trial, making decisions as to the future continuation (or otherwise) of the trial, by monitoring recruitment rates, approving proposals by the TMG concerning any change to the design of the trial, as well as receiving letters of feedback from the independent Data Monitoring Committee (DMC). The DMC comprises a statistician, an academic pharmacist with an interest in patient safety, and an academic GP (Chair) with extensive trials experience. The DMC has a remit to monitor the safety of the trial participants through examination of trial safety and efficacy data, thereby providing advice to the Chair of the Programme Steering Committee (PSC). The DMC Chair informs the Chair of the PSC if, in the view of the DMC, one trial arm is clearly indicated or contraindicated (for all participants or a particular category of participants), and there is a reasonable expectation that this new evidence would materially influence patient management.There is a study Quality Management and Monitoring Plan (version 2: 1 June.2018) which details the procedures for quality control and data monitoring by the NCTU. The study will also be subject to random monitoring by the host Universities and local Research and Development Departments.

A cluster randomized trial. A cluster randomized controlled trial. A cluster randomised controlled trial.