Swansea University
Prifysgol Abertawe

TITLE OF THE PROTOCOL: Medication monitoring in general practice: clinical impact of implementing a nurse-led Adverse Drug Reaction (ADRe) Profile in older adults with 5 or more prescribed medicines

Short title/Acronym: Medication monitoring in general practice/ADReGP

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Faculty **Faculty of Health and Life Sciences**

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STUDY SUMMARY/SYNOPSIS

TITLE	**Medication monitoring in general practice: clinical impact of implementing a nurse-led Adverse Drug Reaction (ADRe) Profile in older adults with 5 or more prescribed medicines**
SHORT TITLE/Acronym	Medication monitoring of older adults with polypharmacy in primary care/ADReGP
Protocol Version Number and Date	V2 08/01/2021
Methodology	Multiple-site parallel arm randomised controlled trial
Study Duration	Jan 2021 – Oct 2022 22 months
Study Centre	GP practices or community nurse-led clinics (Swansea Bay UHB, Hywel Dda UHB and Cardiff & Vale UHB)
Objectives	• To establish the suitability/effectiveness of ADRe Profile for video call completion • To establish whether patients could complete parts of ADRe Profile themselves • To explore whether the ADRe Profile identifies health problems that could be attributable to polypharmacy and ameliorated (and record any changes to care, benefits or harms to the patients) • To explore whether routinely collected data could be used to populate the ADRe Profile
Number of Subjects/Patients	131 (35 – validity testing, 80 – patients, 16 – healthcare professionals)
Main Inclusion Criteria	**Phase 1** • **Content validity index respondents**: healthcare professionals (current or retired, working full-time or part-time, willing to

	participate), service users (age > 64, willing to participate) • **Cognitive interview respondents**: healthcare professionals (current or retired, working full-time or part-time, willing to participate), service users (age > 64, willing to participate) • **Contrast group validity respondents**: group A (people, age >64, no daily prescribed medicines - vitamin and nutritional supplements and moisturising skin preparations will not be counted as 'medicines', willing to participate), group B (as below) • **Inter-rater reliability and feasibility participants**: service users (age > 64 years, with a long-term condition, prescribed > 5 medications daily. (Vitamin and nutritional supplements and moisturising skin preparations will not be counted as 'medicines'.), Willing and able to give informed, signed consent themselves, or where capacity is lacking in the opinion of their nurses, a consultee/representative accompanying the patient who is willing to give advice and assent to the service user participating and sign on their behalf. **Phase 2** **Service users:** • age > 64 years • with a long-term condition • prescribed > 5 medications daily. (Vitamin and nutritional supplements and moisturising skin preparations will not be counted as 'medicines'.) • Willing and able to give informed, signed consent themselves, or where capacity is

	lacking in the opinion of their nurses, a consultee/representative accompanying the patient who is willing to give advice and assent to the service user participating and sign on their behalf. **Nurses:** • Working in or alongside a general practice and expected to work there for the next 6 months **Pharmacists and GP's:** • Aligned with the general practice, expected to stay in employment for the next 6 months **Phase 3** No new participants, we shall approach people who took part in Phase 2.
Statistical Methodology and Analysis	We are combining quantitative and qualitative methods of analysis to capitalize on the respective strengths of each of the approaches. The mixed methods will help to evaluate the intervention effect from a patient perspective, as well illustrate the conclusions derived from the quantitative data with stakeholder insight (Bharmal et al., 2018). The overall design is sequential: QUAN Phase 1 informs QUAN + QUAL Phase 2, which informs convergent design Phase 3 (QUAN + QUAL), Itemised methods of analysis are described below: **Content Validity Index (CVI)** To be measured using Lynn's (1986) method: Experts will rate each item using a four-point ordinal scale (1 = not relevant, 2 = somewhat relevant, 3 = quite relevant, and 4 = highly relevant) Number of experts rating the item 3 or 4 will be divided by total number of experts Result of 0.78 or above will be accepted as having met the validity threshold. Scale content validity ratio will be calculated as a proportion of total items judged against content valid items.

	Cognitive interviews Think aloud technique combined with participant confidence rating (the degree of confidence participant has in their answer) and observation (eg. To find out where people start reading, whether they look for instructions, whether they take longer to answer any particular questions) **Contrast group construct validity** Numerical value will be added to ADRe responses (0 for 'no' answers and 1 for 'yes' or 'worse' answers. Numbers of problems will be compared for the group (n=20) without prescribed medicines and the group (n=20) that is prescribed > 4 medicines (these are participants of 1.2 ADRe testing). **Inter-rater Reliability (IRR)** Cohen's Kappa will be calculated (Cohen, 1960) to compare patient and researcher completion. **Randomised Controlled Trial** Data will be entered into excel via the electronic version of ADRe, imported into SPSS and described for the before and after ADRe administrations. Statistical analysis: differences between before and after the intervention will be calculated for: number and nature of problems addressed, prescription regimens, NHS use. The impact of GP practice, age, diagnoses, and medicines' use (numbers and types of medicines prescribed) will be described and accounted for. To explore the recorded changes and potential for further clinical gains, putative aetiologies of service users' signs and symptoms will be ascribed, using clinical information from medical and nursing records, including, but not restricted to, information on ADRe, and the list of medications prescribed (and over the counter) The ascription will be checked by supervisors using manufacturers' literature and formularies. Juxtaposition of ADRe and medication lists will generate suggestions for changes to improve the processes and possibly the

	outcomes of care. The prevalence of problems on the before and after profiles will be compared with two by two contingency tables, using McNemar's test for related dichotomous variables (Altman 1991). **Survey** Data will be described using the Statistical Package for Social Sciences (SPSS) and later combined with the interview results. **Interviews and recorded ADRe consultations** All interviews (and relevant parts of ADRe consultations) will be transcribed verbatim by the researcher/professional transcriber and anonymised. Transcripts will be coded, categorised, analysed and interpreted alongside the data of all completed cases, to identify, analyse and report patterns within data (Braun and Clark, 2006). The transcripts will be analysed by the team using the constant comparative method which will provide a systematic, re-iterative way of comparing and contrasting emerging codes, categories and concepts and ensure that theoretical perspectives are embedded in the description of change. Two researchers (VL, SJ) will ensure validity of the analysis and verify interpretation. Disagreements will be resolved through discussion at team meetings. Diaries/logs will also be analysed in association with interview transcripts. Triangulation Survey and interview data will be integrated with the outcome measures documented on the ADRe Profile, taking a pragmatic perspective of complementary triangulation (Östlund et al., 2011). Resulting cross-cutting themes derived from the data should enhance understanding and validity, and contextualise the ADRe data (Foss & Ellefsen, 2002; Denzin, 2012). **Costs** Resource use, costs, and health economic outcome measures will be described using the Personal

	Social Services Research Unit (PSSRU) unit costs of health workers (www.pssru.ac.uk) and the National Tariff Payment Systems. The regulatory and governance requirements will be met through gaining approval from the relevant review bodies to conduct the project.

Protocol Agreement Page

The clinical study as detailed within this research protocol

(Version 2, dated 8th January, 2021),

or any subsequent amendments will be conducted in accordance with the

- UK Policy Framework for Health and Social Care Research (2017)
- Medicines for Human Use (Clinical Trials) Regulations (2004)
- Medical Devices Regulations (EU MDR/IVDR 2017)

World Medical Association Declaration of Helsinki (1996)

and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

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Glossary of Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
EC	European Commission
GAfREC	Governance Arrangements for NHS Research Ethics Committees
ICF	Informed Consent Form
ISRCTN	International Standard Randomised Controlled Trial Number
MA	Marketing Authorisation
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principle Investigator
QA	Quality Assurance
QC	Quality Control
Participant	An individual who takes part in a clinical trial
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee

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1. Introduction

1.1 Background

Medicines' management, especially monitoring therapeutic and adverse effects for older adults, is an area of growing importance (Care Quality Commission, 2019; NHS Scotland, 2018; NICE, 2015; Oscanoa et al., 2017; WHO, 2017, 2019). Medicines prescribed for the older population can lead to medicine-related frailty (Saum et al., 2017) and adverse drug reactions due to polypharmacy and altered pharmokinetics (Chetty et al., 2018). Adverse drug reactions cause around 5-8% of unplanned hospital admissions in the UK, costing the NHS £1.5-2.5bn pa (NICE, 2015), apart from the avoidable patient harm.

GP's are increasingly prescribing more medications that would have been prescribed by specialists in the past (Wood, 2020). GMC published in its report Investigating the prevalence and causes of prescribing errors in general practice that 1 in 20 prescriptions contained an error in terms of medication or monitoring, affecting 1 in 8 patients (2012). It is well known that the number of people with multiple conditions is increasing, with older people more likely to live with a long-term disease (Health Foundation, 2018). The problems persist, and polypharmacy presents a major threat to patient safety internationally (WHO, 2019).

Many adverse drug reactions could be prevented with improved monitoring (Gabe et al., 2011). Doctors, pharmacists and nurses are regularly involved with aspects of medicine management, yet there is often a lack of clarity in who should monitor for the side effects and both doctors and nurses think that the other profession monitors patients for adverse effects of prescribed medicines (Logan et al 2020). ADRe Profile (Jordan et al 2014; Jordan et al 2015) represents an innovative nurse-led tool, which collates patient observation and self-reported data to identify a potential link of any problems with the medicines prescribed.

1.2 Preclinical Data

The study population are older people who are prescribed 5 or more medications daily. Implied is the presence of one or more long-term conditions, particularly cardiovascular, respiratory, endocrine, neurological, mental health and musculoskeletal conditions. Implementation of guidelines for management of these conditions results in prescriptions. An increase in the number of long-term conditions increases the complexity of therapeutic and pharmacological management and is associated with the use of multiple medications. Globally, the numbers of older people are growing and more live with multimorbidity (WHO, 2016). The UK incidence of long-term health problems in people older than 65 years was 8.75 million in 2019 (Office for National Statistics [ONS], 2020). This translates to over 2 in 3 people over 65 having a long-term condition. In England, simulation projections estimate that between 2015 and 2035, the number of older people with more than 4

diseases will double and a third of these will have mental health problems (Kingston et al., 2018). Polypharmacy is hence a phenomenon that likely to increase (Duerden et al., 2013) and medication safety has been identified as the theme of the WHO third global safety challenge (WHO, 2017).

1.3 Clinical Data

Medication monitoring and monitoring patients for potential adverse drug reactions has been described as an 'orphan task' in the past due to its position on the interprofessional boundary between pharmacy, medicine and nursing and the subsequent deficiency in ownership (Jordan, 2002, Jordan et al., 2016). Recent studies confirm the lack of clarity of the nurses' roles in medication management (De Baetselier et al., 2019) and effective teamwork has been affirmed as a facilitator of safe management of polypharmacy (WHO, 2019), and medication management overall (WHO, 2017). ADRe Profile is an instrument that involves nurses, pharmacists, prescribers and patients in monitoring for adverse drug reactions to medicines. Nurses and patients identify the problems and may solve some of them, pharmacists review the medicines and prescribers may be provided with recommendations to consider adjustment of the prescriptions.

To date, two randomised controlled trials and five observational/before and after studies have investigated the clinical impact of the ADRe Profile. In total, 168 study participants had the ADRe Profile implemented. Majority of the participants were prescribed mental health medicines (antipsychotics, antidepressants or anti-epileptics), one study included patients with respiratory diseases, taking bronchodilators, corticosteriods or leukotriene receptor antagonists. The setting was mostly in the community, with 3 nursing homes, 3 community mental health settings and one outpatient respiratory clinic.

In two of the community mental health settings, the mean number of problems actioned increased from 0.35 with no ADRe Profile to 3 with ADRe Profile (Jordan et al., 2002; Jordan, 2002). Little change in the number of problems actioned was noted in the comparator groups. The mean number of problems detected increased from 2 without the Profile to 9 with the Profile in one of the studies (Jordan, 2002), no information was offered in the other study. Most actions taken were to alleviate physical health problems.

Another study from an acute mental health service setting identified and addressed health problems for all participants (the mean increase of actions taken was 11.9, SD = 4.7, range 2-20) (Jones et al., 2016). Some of the problems identified were orthostatic hypotension, hypertension, constipation or inadequate diet, two of the

problems were potentially life-threatening (cardiac arrhythmia with chest pain and breathlessness and valproate-induced pancreatitis).

The findings of the three studies from care homes are consistent with the above. 11 participants in a private sector nursing home had at least one problem ameliorated (mean = 4.9, SD = 3.6, range = 1-11), for example previously un-noticed abnormal movements, postural hypotension and pain (Jordan et al., 2014). Majority of residents in the other two care home studies had at least one problem ameliorated. The use of the Profile prompted documentation and treatment of pain, balance, cognitive decline, irritability and other problems (Jordan et al., 2015) and resulted in effective analgesia (7 out of 8 residents with reported pain), amelioration of sedation, confusion or hallucinations (on discontinuation of antipsychotics), changes to care to prevent further falls (5 out of 9 residents with identified falls) (Jordan et al., 2019). Jordan and colleagues (2015) also report a reduction in mental health prescriptions associated with the use of the Profile (aOR 4.45, 1.15-17.22), even though total number of medicines prescribed has not changed, partly due to increase in analgesia.

A trial in a nurse-led respiratory outpatient clinic (Gabe et al., 2014) reported more problems identified and actions taken to ameliorate the problems for the ADRe Profile intervention arm. Examples of problems identified was muscular weakness and pain, dry mouth/dental/oral problems, tendency to bruising and others.

In all studies, the use of ADRe Profile resulted in identification of previously unattended problems and empowerment of the nurse to initiate actions to address the problems. No harm from completing the checklist has been recorded. The ADRe Profile positively contributed to the quality and safety of care.

1.4 Rationale and Risks/Benefits

This study concerns optimisation of medicines monitoring and multidisciplinary team involvement in medicines management and optimisation. Similar projects have not encountered major ethical, legal or management issues, and we do not envisage any here. The Adverse Drug Reaction (ADRe) Profiles for nurse-led medicines monitoring have benefitted patients in all previous trials and observation studies and no harms have been reported. In this study, the instrument will be adapted for use in general practices and the feasibility of its adoption will be explored by the researchers. The ADRe Profile has recently been endorsed by the Royal Pharmaceutical Society and All Wales Medicines Strategy Group (AWMSG). Embedding the ADRe Profiles thus represents an addition of an established

instrument to the nursing documentation and the risk of physical and emotional harm from the instrument is predicted to be minimal, and no more than in routine clinical interviews. Vital signs will be recorded. Results of ECGs, lung function tests and laboratory results will be noted as 'present / absent': these tests are not part of the study.

Risks and burdens according to study participants:

Content validity index and construct validity respondents: we foresee no potential risk of physical or emotional harm to competent adult respondents completing an electronic document from their own computers in their own time.

Cognitive interview participants: we foresee no potential risk of physical or emotional harm to competent adult respondents reading through a draft instrument with a trained research fellow in their own time. Respondents will be asked questions on validity and interpretation of the instrument. They will not be asked any questions about themselves or expected to divulge any personal information. No identifiable data will be collected.

Service users – ADRe Profile completion: Previous work in the nursing homes and a respiratory clinic indicates that no physical or emotional harms emanate from this intervention, and the physical health of all participants has benefitted (Gabe et al., 2014; Jordan et al., 2015; Jones et al., 2016; Jordan et al., 2019). We do not foresee any risks of physical or emotional harm in this or future studies. We foresee no legal or organisational risk from this study. Any changes to patient management will be based on the professional judgment of staff delivering routine care, and not directed by the study procedures. The intervention only aims to enhance patient monitoring to inform professional judgement. All questions and observations are of a nature that should be pursued under routine care. Time will be required by nurses to complete the ADR profiles; however, the clinical gains reported in care home studies are likely to outweigh any diversion of resources (Jordan et al., 2015, 2014, 2019). Should any answers in the ADRe Profile raise the nurse-researcher's concern about physical or mental health and well-being of the participant, clinical judgment will be applied and the participant will be advised or referred to their general practitioner. Completed ADRe profiles will be passed to the pharmacist associated with the GP practice and academic pharmacists and thence prescribers.

Balance of risks and benefits of participation in the ADRe Profile completion:

Risk	Benefit
- Breach of confidentiality - Adjustment of medicines, additional prescriptions or de-prescribing - Possible additional health service contacts - Possible misunderstanding (esp. people who have difficulty speaking or understanding English)	- Additional medication review - Potential identification and amelioration of health and well-being problems - Opportunity to discuss therapeutic regimen with academic clinicians, and access ADRe's supporting information.

Survey and semi-structured interviews: stakeholder perspectives will be sought from service users, nurses, pharmacists and GP's. There are no significant risks attached to these interviews, however; should any participant become upset/distressed during the interviews, the researcher, who is experienced at de-escalating difficult/emotional situations, will deal with the situation. Potential risks and burdens will be described in the participant information sheet in such a way that participants can clearly understand what will be involved if they consent to take part. The principles of GCP training and the standard operating procedures of the Swansea Clinical Trials Unit will be followed throughout. The trials unit has granted access to their standard operating procedures.

Covid 19 pandemic: The researchers will ensure compliance with health and safety requirements in the context of the pandemic, and measures that adhere to current infection control guidelines (e.g. protective equipment, social distancing). Alternative arrangements have been planned to protect the potentially vulnerable participants from the effects of Covid 19. If by the time the trial is taking place it would be deemed that in-person exposure would increase the participants' risk of contracting Covid 19, all contact will be only electronic, through video calls, phone calls or by post. We will be guided by Welsh government responses to the pandemic.

2. Trial Objectives and Design

2.1 Trial Objectives

Primary Objectives

- To establish the suitability/effectiveness of ADRe Profile for video call completion
- To establish whether patients could complete parts of ADRe Profile themselves
- To explore whether the ADRe Profile identifies health problems that could be attributable to polypharmacy and ameliorated (and record any changes to care, benefits or harms to the patients)
- To explore whether routinely collected data could be used to populate the ADRe Profile

Secondary Objective

- To establish the validity and reliability of the ADRe Profile
- To explore the feasibility of linking the electronic ADRe Profile to GP electronic records
- To report how ADRe Profile contributes to efficient collaboration of the multiprofessional team (nurses, care assistants, pharmacists, GP's) in monitoring the effects of patients' medications
- To report how ADRe contributes to patient-centered care
- To estimate costs associated with ADRe implementation

Primary Endpoint

Phase 1

- Content validity index (overall assessment of validity of the instrument)
- Construct validity (overall assessment of validity of the instrument)
- Cognitive interviews: Enhanced understanding how participants answer the ADRe questions.
- Inter-rater reliability of patient versus nurse-researcher completed ADRe Profile (Cohen's Kappa) - (To determine how much of the potential variability of the records is due to errors in measurement, to estimate a degree to which service users accurately evaluate their symptoms when compared with a nurse researcher, to determine suitability of ADRe for patient self-completion. Cohen's Kappa will be calculated.) [Time Frame: 4 months from the start of the study]
- Level of completion of all items in the video call-completed ADRe Profile. (Comparison of completeness of the ADRe Profile completed through a video

call with ADRe Profiles previously completed in person, suitability of ADRe Profile for video call completion.) [Time Frame: 4 months from the start of the study]

- Calculated percentage and described nature of items on the ADRe Profile that can be populated from accessing the nursing and medical notes. (Establishing the overlap of information - the number and nature of the ADRe items that have previously been collected and recorded in the patients' nursing and medical notes.) [Time Frame: 16 months from the start of the study]

Phase 2

- Clinical impact on service users, including new problems identified (number and nature) and problems addressed (number and nature). [Time Frame: 16 months from the start of the study]
- Number of patients with a change in signs and symptoms related to adverse effects of prescribed medicines. Care quality/ clinical gain/ benefit to patients as recorded in notes and on the Profile by the number and nature of all health problems addressed, particularly serious adverse events. [Time Frame: 16 months from the start of the study]
- Prescription changes (number of patients with changes in prescription regimens: drug or dose. Number and nature of changes). [Time Frame: 16 months from the start of the study]

Phase 3

- Description of stakeholder views on ADRe Profile implementation effectiveness (survey rating of the ADRe Profile - Likert scale). A brief survey will be distributed to the main stakeholders (patients, nurses, GP's and pharmacists) following completion of Randomised Controlled Trial. [Time Frame: 22 months from the start of the study]
- Description of stakeholder views on ADRe Profile implementation feasibility (eliciting interview themes). Semi-structured interview with the main stakeholders (patients, nurses, GP's and pharmacists) to explore their views on feasibility of ADRe Profile integration in GP practices. [Time Frame: 22 months from the start of the study].

Secondary Endpoint

- Calculation of the average nurses', GP's and pharmacists' length of time per one ADRe Profile completion. Average length of the health professionals' time involvement with one ADRe Profile. [Time Frame: 16 months from the start of the study]. Phase 2
- Calculation of the cost of nurses', GP's and pharmacists' time, based on average national salary cost per hour. Estimated costs of ADRe implementation in GP practices. [Time Frame: 16 months from the start of the study] Phase 2

- Description of the main stakeholders' views on multidisciplinary collaboration (eliciting interview themes). Semi-structured interview with the main stakeholders (patients, nurses, GP's and pharmacists) to explore their views on whether and how ADRe Profile contributed to multidisciplinary collaboration between nurses, doctors and pharmacists. [Time Frame: 22 months from the start of the study] Phase 3
- Description of the patients' views on the contribution of ADRe Profile to patient-centered care (eliciting interview themes). Semi-structured interview with the patients to seek their views on whether and how ADRe Profile contributes to patient-centered care. [Time Frame: 22 months from the start of the study] Phase 3

2.2 Trial Design

Phase 1

- Validity testing: content validity index (CVI), cognitive interviews, construct validity testing
- Feasibility trial
- Reliability testing (inter-rater reliability)

Phase 2

- Randomised controlled trial (cluster group randomization by GP practice, intervention arm (ADRe Profile implementation), control arm (standard of care)

Phase 3

- Interviews and survey with participants of phase 2

2.3 Study Scheme Diagram

Figure 1: study scheme diagram

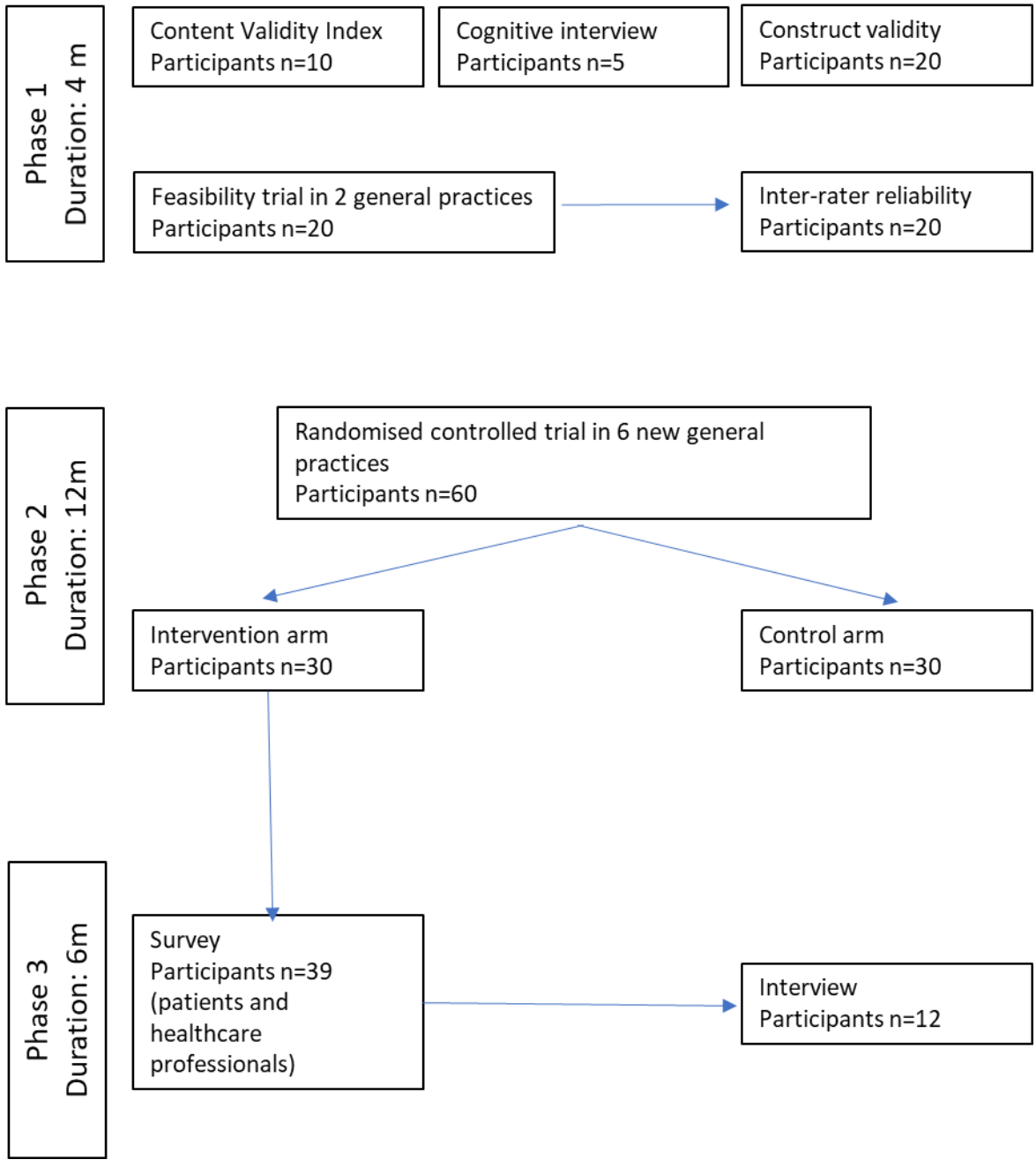
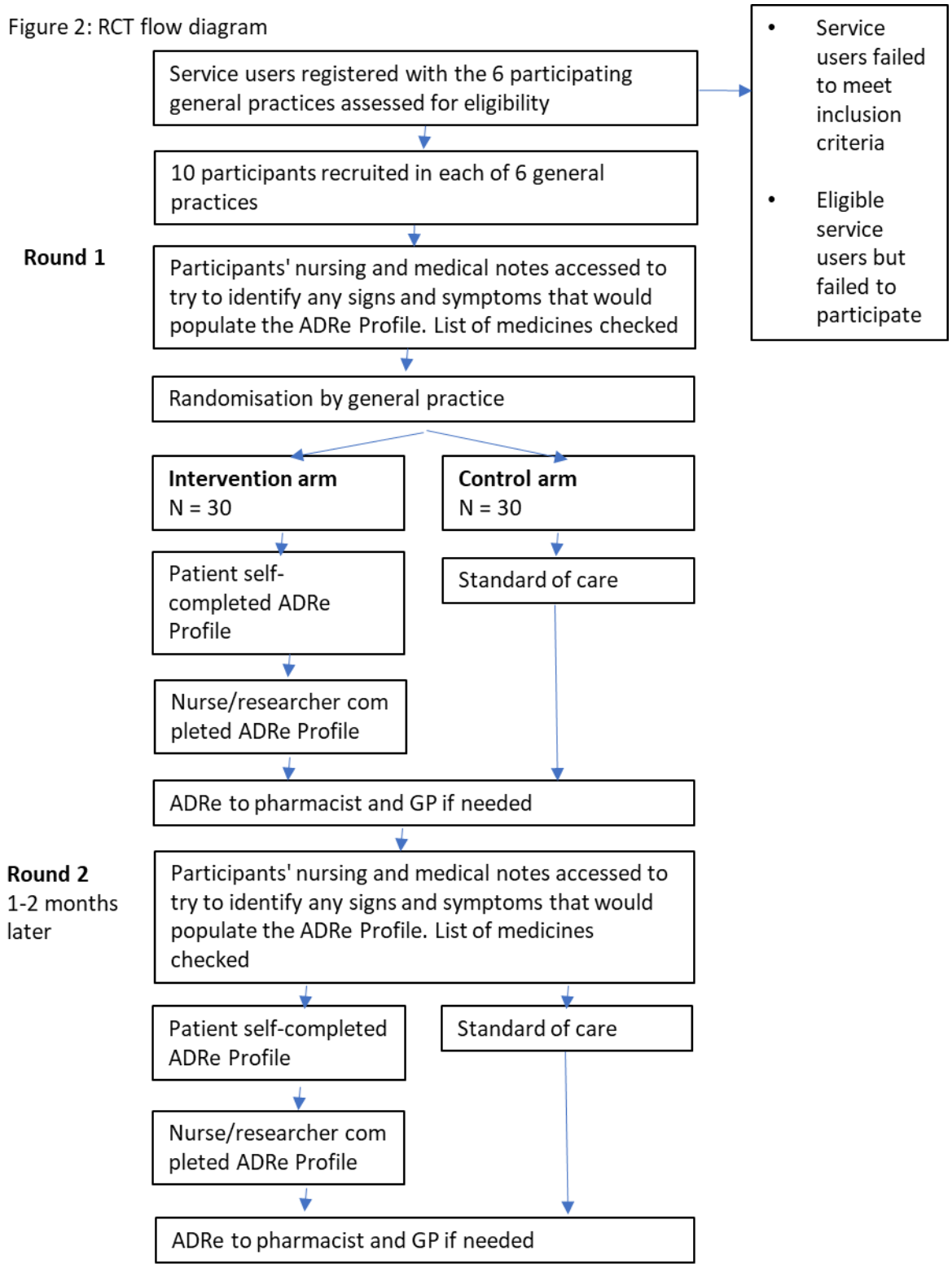


Figure 2: RCT flow diagram



3. Subject Selection

3.1 Number of Subjects and Subject Selection

Content Validity Index sample size n = 10
Participants: a convenience sample of 2 GPs, 2 pharmacists, 2 nurses working in general practice/community and 2 care assistants working in general practice/community and 2 patients
Recruitment strategy: advertise in research networks and the university

Contrast group sample size n = 2x20
Participants: a convenience sample of up to 20 service users > 64 who do not take prescribed medicines daily.
Recruitment strategy: Advertise in research networks and the university

Cognitive interview sample size n = 5
Participants: a convenience sample of 1 patient, 1 nurse working in general practice/community, 1 care assistant working in general practice/community, 1 GP + 1 pharmacist
Recruitment strategy: Advertise in research networks and the university

Inter-Rater Reliability sample size n = 20 + 30 = 50
Participants: 20 service users from 2 general practices, >64, with >4 prescribed medicines.
Recruitment strategy: Approach cluster areas in Swansea Bay UHB and Hywel Dda UHB. Invitation by letter and/or email. General practice to identify suitable patients and approach them to invite for participation.

Randomised Controlled Trial sample n = 60
Participants: 6 new general practices x 10 patients and practice / district nurses or nurse assistants

Recruitment strategy: approach all 8 GP clusters in Swansea Bay UHB and 7 clusters in Hywel Dda UHB by post and/or email. General practice to identify suitable patients and approach them to invite for participation.

Calculation of the sample size:

RCT (sample = 60): Previously, in a 'before and after' single arm intervention study, with participants acting as their own controls, 17/19 (89%) had improvement in at least 1 clinical problem when ADRe Profiles for polypharmacy were used (Jordan et al submitted). We hypothesised that 9/19 (47%) would have shown some improvement without intervention, necessitating an effective sample of 40 patients (20 in each arm), with 5% significance and 90% power (Uitenbroek 1997). Based on the reported intra-cluster coefficient (0.02), (Jordan et al 2015), and a design effect of 1.18, to achieve an effective sample size of 40, we need an actual sample size of 48 (Killip et al 2004). 10 patients in each of 6 clusters (GP practices) allows for 20% loss to follow up, which is realistic in general practice, where either patient or nurse may be unavailable for follow up.

Survey sample size: up to 3 nurses, 3 pharmacists, 3 GP's and up to 30 service users.

For the survey, all health professionals involved with the intervention arm (n=9) and all service users in the intervention arm (n=30) will be included. The aim is to gain stakeholder views on the intervention.

Qualitative semi-structured interviews sample size - 3 nurses, 3 pharmacists, 3 GP's and 3 service users

For the qualitative interviews, a convenience sample of 12 participants will be selected. This will include all nurses, GP's and pharmacists in the intervention arm, as well as a purposive sample of 3 patients. The patients will be selected based on the most positive and most negative responses in the survey. The aim is to gain stakeholder views on the intervention and to supplement and illustrate the RCT data.

3.2 Inclusion Criteria

Phase 1

- **Content validity index respondents**: healthcare professionals (current or retired, working full-time or part-time, willing to participate and sign informed consent), service users (age > 64, willing to participate)
- **Cognitive interview respondents**: healthcare professionals (current or retired, working full-time or part-time, willing to participate), service users (age > 64, willing to participate and sign informed consent)
- **Contrast group validity respondents**: group A (people, age >64, no daily prescribed medicines - vitamin and nutritional supplements and moisturising skin preparations will not be counted as 'medicines', willing to participate and sign informed consent), group B (as below)
- **Inter-rater reliability and feasibility participants**: service users (age > 64 years, with a long-term condition, prescribed > 5 medications daily. (Vitamin and nutritional supplements and moisturising skin preparations will not be counted as 'medicines'.), Willing and able to give informed, signed consent themselves, or where capacity is lacking in the opinion of their nurses, a consultee/representative accompanying the patient who is willing to give advice and assent to the service user participating and sign on their behalf.

Phase 2

Service users:

- age > 64 years
- with a long-term condition
- prescribed > 5 medications daily. (Vitamin and nutritional supplements and moisturising skin preparations will not be counted as 'medicines'.)
- Willing and able to give informed, signed consent themselves, or where capacity is lacking in the opinion of their nurses, a consultee/representative accompanying the patient who is willing to give advice and assent to the service user participating and sign on their behalf.

Nurses:

- Working in or alongside a general practice and expected to work there for the next 6 months, willing to participate and sign informed consent

Pharmacists and GP's:

- Aligned with the general practice, expected to stay in employment for the next 6 months, willing to participate and sign informed consent

Phase 3

No new participants, we shall approach people who took part in Phase 2.

3.3 Exclusion Criteria

Phase 1

- **Content validity index respondents:** not willing to participate
- **Cognitive interview respondents:** not willing to participate
- **Contrast group validity respondents:** not willing to participate
- **Inter-rater reliability and feasibility testing respondents: a**ge < 64 years, without any long-term conditions, prescribed < 5 medications daily, not willing to participate, unable to consent and no consultee/representative present, not fluent in English or Welsh (unless a family member can assist with translation), receiving palliative care, expected to remain in the practice for the next 12 months

Phase 2

Service users:

- Age < 64 years
- Without any long-term conditions
- Prescribed < 5 medications daily
- Not willing to participate
- Unable to consent and no consultee/representative present
- Not fluent in English or Welsh (unless a family member can assist with translation)
- Receiving palliative care

- Expected to remain in the practice for the next 12 months

Nurses:

- Unwilling to participate, unwilling to administer ADRe Profile

Pharmacists and GP's:

- Unwilling to participate, unwilling to review ADRe Profile

Phase 3

No new participants.

Recruitment and identification of personal Consultees: In the event that a participant lacks decision-making capacity regarding participation in the study a personal consultee will be identified to provide advice. The Consultee may be their next of kin, family member, a friend, an unpaid carer, other relative in regular contact. The Personal Consultee will have an unpaid or non-professional role in caring for the person.

The consultee will be identified by the practice nurse as they will likely accompany the service user to the GP practice or respond to the invitation to participate on behalf of the service user. The consultee will be contacted to provide a information about the study (Participant Information Sheet for consultees) and they will be asked for their advice regarding the inclusion of the person and what the person's views would have been regarding inclusion in the research if they had capacity to make the decision for themselves. If they are happy to be a Personal Consultee, they will sign the consent form for consultees.

In the event that a Personal Consultee cannot be identified, or is not willing or able to act (for example due to their own illness or infirmity), the service user will not be included in the study.

The Consultees will have as much time as they need to consider the study and will have the opportunity to ask the practice nurse/or the researcher questions before giving their advice regarding the inclusion of the person lacking capacity.

The practice nurse/researcher will obtain written confirmation that the Consultee has provided consent by means of a Consultee dated signature on the Consultee Declaration Form, and dated signature of the person who presented and obtained the declaration.

The original signed form will be retained in the participant's medical records, a copy will be provided to the researcher for the ADRe Study site file in the ADRe office, and copies will be offered to the participant or his/her family and the consultee.

3.4 Criteria for Premature Withdrawal

Parts of the study involve single contact with researcher, so there is little scope for non-compliance (content validity index, cognitive interviews, construct validity, survey, interviews). The feasibility trial (n=20) and the intervention arm of the trial (n=30) involve 3 and 5 points of contact (in person or virtual), respectively. If the participant becomes too unwell to respond to ADRe, and there is no consultee available, they will not be asked to complete a 2nd ADRe. However, unless informed otherwise, we shall retain collected data and collect information from patients' notes as originally planned.

4. Study Procedures

4.1 Informed Consent Procedures

Informed consent will be gained from all research participants. Principal investigator or the practice nurse will take consent,

Arrangements for seeking consent:

In designing the consent process, we aimed for transparency and clarity, and we chose wording that we think reduces the possibility that potential participants feel pressured to join the study due to a sense of moral responsibility.

Consent for the validity and reliability testing will be sought electronically.

Procedure for seeking consent for the feasibility testing, RCT, survey and interview: when expressions of interest are received from potential participants, we shall approach the individuals and arrange a time and format (i.e. virtual or face-to-face) that is preferred and convenient for them and in line with Covid 19 pandemic guidelines. All potential participants will be given an information sheet outlining the purpose of the project and interview and given time to reflect on the study. Help and clarification will be given as needed. During this process the nurse-researcher will make judgements whether the potential participant is able to understand the information relevant to the decision, retain that information, use or weigh up that information as part of the process of making the decision, and communicate their decision. Participants appearing to be competent will be asked to sign a consent form (electronic signature will be accepted). If any doubts arise with regards to competence, the service user's consultee will be approached, if available, or the

decision will be postponed. The service user will not be included in the study if not competent and no consultee/representative available. Consent will be recognised as a continuously negotiated process, which provides opportunities for ongoing communication between the researcher and participant ensuring voluntary and informed participation. For consenting participants, a copy of the consent will be retained in the patient's notes, a copy will be offered to the participant and a copy will be securely stored by the researchers (chief investigator's locked office).

Participant Information Sheets (PIS):

Participant information sheets will clearly explain the study in plain language. A copy given to participants will be kept for future reference. GDRP leaflet and Summary information will be included in PIS. The date PIS has been given to the participant will be recorded in the notes along with the consent form to ensure sufficient length of time for participants to decide on their involvement.

Participants will have as long as needed to decide whether or not they want to take part, maximum of 14 days.

4.2 Screening Procedures

Initial screening will be performed by a member of the potential participant's usual clinical care team. This healthcare professional will keep a screening log record.

4.3 Randomisation Procedures (if applicable)

Randomisation of participants in Phase 2 will be performed to promote internal design validity and minimise the effects of confounding. To avoid selection bias and enable allocation concealment, GP practices will be selected and patients consented before randomization. While masking is not possible due to the design of the study, ascertainment bias will be lowered by researchers not being aware of the randomization results until after they have accessed the nursing and medical notes and elicited necessary data. Cluster randomization will allow each practice its own care as an independent entity and will minimize contamination. The cluster design has been accounted for in the sample size.

4.4 Schedule of Treatment for each visit

Procedure	Number of interventions	Routine	Average time	Who will conduct	Place
PHASE 1					
Consent for CVI	1	no	5 mins	researcher	Electronic
Content validity index	1	0	10 mins	researcher	Electronic
Consent for cognitive interview	1	0	5 mins	researcher	Electronic
Cognitive interviews	1	0	1 hour	researcher	Virtual (video call)
Consent for construct validity testing	1	0	5 mins	researcher	Electronic
Construct validity testing	1	0	10 mins	researcher	Electronic
Consent (+ reading PIS) for service users – PHASE 1	1	0	15 mins – as long as the participant needs	Researchers or nurses	Virtual/GP surgery
ADRe Profile self-completion	1	1	10 – 25 mins	service users	Virtual
ADRe Profile completion with nurse	1	1	10 – 25 mins	Nurse-researchers	Virtual/GP surgery

researcher					
Debrief	1	0	15 mins	researchers	Virtual/GP surgery
PHASE 2					
Consent (+ reading PIS)	1	0	15 mins – as long as the participant needs	Researchers or nurses	Virtual/GP surgery/patient's home
Introductory training for nurses	1	0	15 mins	Researcher	Virtual/GP surgery
ADRe Profile self-completion	2	1	10 – 25 mins	service users	electronically or by post
ADRe Profile completion with a nurse/nurse-researcher	2	1	10 – 25 mins	nurse/researchers	Virtual/GP surgery/patient's home
Debrief	1	0	15 mins	researchers	Virtual/GP surgery/patient's home
PHASE 3					
Survey – service users	1	0	10 mins	researchers	Electronic/by post
Survey – GP's	1	0	10 mins	researchers	Electronic/by post
Survey - pharmacists	1	0	10 mins	researchers	Electronic/by post
Survey – nurses/care assistants	1	0	10 mins	researchers	Electronic/by post
Interview -	1	0	1 hour	researchers	Virtual/GP surgery/patient's

service users					home
Interview – GP's	1	0	1 hour	researchers	Virtual/GP surgery
Interview - pharmacists	1	0	1 hour	researchers	Virtual/GP surgery
Interview – nurses/care assistants	1	0	1 hour	researchers	Virtual/GP surgery
Debrief /feedback	1	1	10 mins	researcher	Virtual/GP surgery

4.5 Schedule of Assessment (in Diagramatic Format)

Phase of study	Intervention arm	Control arm
Phase 1 - feasibility	Medical notes accessed for items to populate ADRe Profile	No control
	Self-completed ADRe Profile	
	Researcher-completed ADRe Profile	
Phase 2 – RCT step 1	Medical notes accessed for items to populate ADRe Profile	Medical notes accessed for items to populate ADRe Profile
	Self-completed ADRe Profile	Standard of care
	Nurse or researcher-completed ADRe Profile	Standard of care
Phase 2 – RCT step 2	Medical notes accessed for items to populate ADRe Profile	Medical notes accessed for items to populate ADRe Profile
	Self-completed ADRe Profile	Standard of care
	Researcher-completed ADRe Profile	Standard of care
Phase 3 – Survey and interviews	Survey administered to service user participants	
	Interviews performed with selected	

	participants (3 service users, 3 nurses, 3 GP's, 3 pharmacists)	

4.6 Follow up Procedures (if applicable)
N/A

4.7 Laboratory Assessments (if applicable)
N/A

4.8 Radiology Assessments (if applicable)
N/A

4.9 Medical Devices (if applicable)
ADRe Profile is designed to help healthcare professionals detect possible adverse side effects caused by service users' primary care medicines, and review their general health and well-being, in case this has worsened as a result of these medicines. It brings together relevant information and gives the prescriber or pharmacist reviewer a picture of all possible adverse effects and all medicines prescribed.

4.9 End of Study Definition

End of a clinical trial will be the last visit (or virtual visit) of the last subject to complete the ADRe Profile. End of the whole study will be the interview with the last interviewee. The end of the study is estimated to be October 2022 and no later than July 2023.
Criteria for stopping the study early:
- inability to access GP service users, recruit participating GP practices
- serious event precluding principle or chief investigator from finishing the research
- results from phase 1 show no justification for continuing with phase 2, results from phase 2 show no justification for continuing with phase 3.

Once the end of study has been declared, no further substantial amendments will be made and a Clinical Trial Summary Report will be produced. The HRA ethics committee (The 'Declaration of the End of Trial Form' will be completed) and the NHS R&D offices will also be notified within 3 months of the end of the study.

4.11 Procedures for unblinding (if applicable)
N/A

4.12 Subject Withdrawal

Criteria for participant withdrawal:

- participant's /consultee's wishes
- physical deterioration, where continuing with the research would represent a burden on the participant
- failure to engage in participation
- move into long-term care facilities
- prolonged hospitalisation

4.13 Data Collection and Follow up for Withdrawn Subjects

Unless requested otherwise, data that has been already collected will be kept for withdrawn participants.

5. Laboratories (if applicable)

N/A

6. Safety Reporting

6.1 General Definitions

Adverse Event (AE)

An AE is any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with study activities.

Serious Adverse Event (SAE)

An SAE fulfils at least one of the following criteria:

· Is fatal – results in death (NOTE: death is an outcome, not an event)
· Is life-threatening
· Requires inpatient hospitalisation or prolongation of existing hospitalisation
· Results in persistent or significant disability/incapacity
· Is a congenital anomaly/birth defect
· Is otherwise considered medically significant by the Investigator

6.1.1 Adverse Event (AE)

If an adverse event is identified or reported, it will be recorded in the participant's medical records. Any adverse events will be assessed by the clinical team and the chief investigator. Any adverse events arising as a result of the ADRe checklist will be passed to the sponsor's representative and the participant's responsible clinician for assessment. No adverse events have arisen as a result of using the ADRe

checklists in 2 trials and 3 observation studies. Previous research has not identified any harm resulting from completing the ADRe Profile checklist. We are not planning on establishing a Data Monitoring Committee.

6.1.2 Serious Adverse Event (SAE)

Previous research has not identified any harm resulting from completing the ADRe Profile checklist. We are not planning on establishing a Data Monitoring Committee.

6.2 Investigators Assessment

6.2.1 Seriousness

The Chief/Principal Investigator or the clinical team responsible for the care of the patient will assess whether the event is serious.

6.2.2 Causality

The Chief Investigator will be responsible for assessing the causality.

6.2.3 Expectedness

It is unlikely that completing a checklist should cause any serious adverse events.

6.2.4 Severity

The Chief Investigator will assess the severity of the event according to the following definitions:

Mild: Some discomfort noted but without disruption of daily life
Moderate: Discomfort enough to affect/reduce normal activity
Severe: Complete inability to perform daily activities and lead a normal life

6.3 Notification and reporting Adverse Events or Reactions

Any Adverse Event will be recorded in the study file and the participant will be followed up the research team. The Adverse Event will be documented in the participant's medical notes and the CRF.

6.4 Notification and Reporting of Serious Adverse Events

6.4.1

Related and unexpected Serious Adverse Events will be reported to the sponsor within 24 hours of learning of the event and to the Main REC within 15 days.

6.5 Urgent Safety Measures

Should the Chief Investigator need to take any urgent safety measures to ensure the safety and protection of the trial participants from any immediate hazard to their health and safety, any such measures will be taken immediately. The Sponsor and the Main Ethics Committee will be informed immediately via telephone and in writing within 3 days (in a form of a substantial amendment). The Sponsor will be sent a copy of all correspondence.

6.6 Annual Safety Reporting

The Chief Investigator will send the Annual Progress Report to the main REC (using NRES template).

6.7 Procedures for reporting blinded ' unexpected' and related' SAEs

N/A

6.8 Overview of the Safety Reporting Process/Pharmacoviligance responsibilities

It is extremely unlikely that the implementation of the ADRe Profile (checklist) should cause any harm. The ADRe Profile has been developed to identify and support amelioration of potential side effects from commonly prescribed medicines. As part of the study protocol, the completed ADRe Profile and the list of patient's medicines is reviewed by the study pharmacist and, if needed, the patient's GP.

7. Statistical Considerations

7.1 Primary Endpoint Efficacy Analysis

Differences between before and after the intervention will be calculated for: problems addressed, prescription regimens, NHS use, and compared, adjusting for site. The impact of age, diagnoses, and medicines' use (numbers and types of medicines prescribed) will be accounted.

7.2 Secondary Endpoint Efficacy Analysis

N/A

7.3 Safety Endpoints

N/A

7.4 Sample Size

RCT (sample = 60): Previously, in a 'before and after' single arm intervention study, with participants acting as their own controls, 17/19 (89%) had improvement in at least 1 clinical problem when ADRe Profiles for polypharmacy were used (Jordan et

al submitted). We hypothesised that 9/19 (47%) would have shown some improvement without intervention, necessitating an effective sample of 40 patients (20 in each arm), with 5% significance and 90% power (Uitenbroek 1997). Based on the reported intra-cluster coefficient (0.02), (Jordan et al 2015), and a design effect of 1.18, to achieve an effective sample size of 40, we need an actual sample size of 48 (Killip et al 2004). 10 patients in each of 6 clusters (GP practices) allows for 20% loss to follow up, which is realistic in general practice, where either patient or nurse may be unavailable for follow up.

For the survey, all health professionals involved with the intervention arm (n=9) and all service users in the intervention arm (n=30) will be included. The aim is to gain stakeholder views on the intervention.

For the qualitative interviews, a convenience sample of 12 participants will be selected. This will include all nurses, GP's and pharmacists in the intervention arm, as well as a purposive sample of 3 patients. The patients will be selected based on the most positive and most negative responses in the survey. The aim is to gain stakeholder views on the intervention and to supplement and illustrate the RCT data.

7.5 Statistical Analysis

We are combining quantitative and qualitative methods of analysis to capitalize on the respective strengths of each of the approaches. The mixed methods will help to evaluate the intervention effect from a patient perspective, as well illustrate the conclusions derived from the quantitative data with stakeholder insight (Bharmal et al., 2018).

The overall design is sequential: QUAN Phase 1 informs QUAN + qual Phase 2, which informs convergent design Phase 3 (QUAL + quan), Itemised methods of analysis are described below:

Content Validity Index (CVI)

To be measured using Lynn's (1986) method:

Experts will rate each item using a four-point ordinal scale (1 = not relevant, 2 = somewhat relevant, 3 = quite relevant, and 4 = highly relevant)

Number of experts rating the item 3 or 4 will be divided by total number of experts

Result of 0.78 or above will be accepted as having met the validity threshold.

Scale content validity ratio will be calculated as a proportion of total items judged against content valid items.

Cognitive interviews

Think aloud technique combined with participant confidence rating (the degree of confidence participant has in their answer) and observation (eg. To find out where people start reading, whether they look for instructions, whether they take longer to answer any particular questions)

Contrast group construct validity

Numerical value will be added to ADRe responses (0 for 'no' answers and 1 for 'yes' or 'worse' answers. Numbers of problems will be compared for the group (n=20) without prescribed medicines and the group (n=20) that is prescribed > 4 medicines (these are participants of 1.2 ADRe testing).

Inter-rater Reliability (IRR)

Cohen's Kappa will be calculated (Cohen, 1960) to compare patient and researcher completion.

Randomised Controlled Trial

Data will be entered into excel via the electronic version of ADRe, imported into SPSS and described for the before and after ADRe administrations. Statistical analysis: differences between before and after the intervention will be calculated for: number and nature of problems addressed, prescription regimens, and NHS use. The impact of GP practice, age, diagnoses, and medicines' use (numbers and types of medicines prescribed) will be described and accounted for in exploratory bivariate and multivariate regression analyses. To explore the recorded changes and potential for further clinical gains, putative aetiologies of service users' signs and symptoms will be ascribed, using clinical information from medical and nursing records, including, but not restricted to, information on ADRe, and the list of medications prescribed (and over the counter) The ascription will be checked by supervisors using manufacturers' literature and formularies. Juxtaposition of ADRe and medication lists will generate suggestions for changes to improve the processes and possibly the outcomes of care. The prevalence of problems on the before and after profiles will be compared with two by two contingency tables, using McNemar's test for related dichotomous variables (Altman 1991).

Survey

Data will be described using the Statistical Package for Social Sciences (SPSS) and later combined with the interview results.

Interviews and recorded ADRe consultations

All interviews (and relevant parts of ADRe consultations) will be transcribed verbatim by the researcher/professional transcriber and anonymised. Transcripts will be

coded, categorised, analysed and interpreted alongside the data of all completed cases, to identify, analyse and report patterns within data (Braun and Clark, 2006). The transcripts will be analysed by the team using the constant comparative method which will provide a systematic, re-iterative way of comparing and contrasting emerging codes, categories and concepts and ensure that theoretical perspectives are embedded in the description of change. Two researchers (VL, SJ) will ensure validity of the analysis and verify interpretation. Disagreements will be resolved through discussion at team meetings. Diaries/logs will also be analysed in association with interview transcripts.

Triangulation

Survey and interview data will be integrated with the outcome measures documented on the ADRe Profile, taking a pragmatic perspective of complementary triangulation (Östlund et al., 2011). Resulting cross-cutting themes derived from the data should enhance understanding and validity, and contextualise the ADRe data (Foss & Ellefsen, 2002; Denzin, 2012).

Costs

Resource use, costs, and health economic outcome measures will be described using the Personal Social Services Research Unit (PSSRU) unit costs of health workers (www.pssru.ac.uk) and the National Tariff Payment Systems.

The regulatory and governance requirements will be met through gaining approval from the relevant review bodies to conduct the project.

8. Data Handling & Record Keeping

8.1 Confidentiality

The Caldicott principles have been followed as an ethical framework for use of identifiable data.

We will only collect data that is necessary for answering the research question and all data will be de-identified and patient numbers/codes used.

Participants will be informed in the Participant Information Sheet about how their data will be handled and processed. They will also be informed of who will have access to the data.

The research involves access to patient data: we shall remain mindful of the risks for patients associated with any breach of confidence or failure to maintain data security. The study team will respect confidentiality of personal data and meet the

requirements of the GDPR regulations and the Data Protection Act, 2018. The research fellow is a registered nurse, recognises the common law duty of confidentiality and is bound by professional code of conduct (NMC, 2018). Completed ADRe Profiles will be either collected electronically (with access secured using the University's login system), or will be returned by post. No identifiable data will be collected on the Profile, only a code number, m/f and age. All data files and transcripts of the interviews/relevant parts of ADRe consultations will be pseudonymised and de-identified before analysis. All data analysis will be performed by the research team.

In interviews and ADRe consultations, we shall try not to collect or transcribe, and will delete from recordings and transcripts, all names, addresses, postcodes, birth dates, ages, salaries, identification numbers, location data of interviews and organisations, online identifiers or references to factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of respondents or organisations. Omissions and redactions will be marked []. Digital recordings from the recording devices will be transferred to a password-protected single user PC for anonymization, transcription and storage. Any transcriptions of interviews and relevant parts of ADRe consultations will be performed by the research team/professional transcriber. Interviews will be assigned numbers and pseudonyms will be used if necessary. Transcripts will be anonymised and de-identified in accordance with the ICO (2012) guidelines (A38). Every interview that has been anonymised and analysed will be saved in a separate Word file. During the analysis, code labels will be applied to the text. The chief investigator will keep an anonymised code table in a Word file on the work computer (secured with password).

In addition, we shall not, for all participants, collect genetic data, biometric data, tissue samples, or data concerning a natural person's sex life or sexual orientation. Data concerning health will not be collected from healthcare professionals and patients responding to CVIs and cognitive interviews (ICO 2012, MRC 2018).

Any disclosures at interview will be treated in strict confidence. We shall avoid disclosure of attributable data in publications. Study numbers will be used throughout. All research participants will be given an information sheet detailing the

use of their data. They will also be asked to sign consent forms when they have read and considered the information sheets.

A log of changes made to anonymise the data will be kept on password protected single user PCs of the chief investigator.

The researchers accept the professional, public, institutional and personal responsibility associated with conducting research. The sponsor of the study – Swansea University – is a signatory to the Concordat to Support Research Integrity (2019), and the expected ethical and procedural standards will be observed. The research fellow is further bound by professional code of conduct (NMC, 2018) and completed Swansea University statutory research training and GCP training (training file available on request).

8.2 Study Documents

- A signed protocol and any subsequent amendments
- Current Summary of Product Characteristics/ Investigator's Brochure
- Sponsor Self-Monitoring template for the trial team to complete on a regular basis as detailed by the Monitoring section
- Current/Superseded Patient Information Sheets (as applicable)
- Current/Superseded Consent Forms (as applicable)
- Indemnity documentation from sponsor
- Conditions of Sponsorship from sponsor
- Conditional/Final R&D Approval
- Signed site agreement
- Ethics submissions/approvals/correspondence
- CVs of CI and site staff
- Laboratory accreditation letter, certification and normal ranges for all laboratories to be utilised in the study
- Delegation log
- Staff training log
- Site signature log
- Patient identification log
- Screening log
- Enrolment log
- Monitoring visit log
- Protocol training log
- Correspondence relating to the trial

- Communication Plan between the CI/PI and members of the study team
- SAE reporting plan for the study

8.3 Case Report Form

Swansea Trials Unit's forms will be adapted for use in CRF (with permission)

1 List of ADReGP Case Report Forms

Number	Title
FORM 01	Inclusion Criteria
FORM 02	Exclusion Criteria
FORM 03	Eligibility review
FORM 04	Randomisation/Enrolment
FORM 05	Patient Details (age and gender)
FORM 06	Baseline Medical Conditions
FORM 07	Baseline Medication list
FORM 08	Baseline ADRe Profile from available medical notes
FORM 09	Baseline Self-completed ADRe Profile
FORM 10	Baseline Nurse/researcher-completed ADRe Profile
FORM 11	Endpoint Medical Conditions
FORM 12	Endpoint Medication list
FORM 13	Endpoint ADRe Profile from available medical notes
FORM 14	Endpoint Self-completed ADRe Profile
FORM 15	Endpoint Nurse/researcher-completed ADRe Profile
FORM 16	Adverse Events
FORM 17	Serious Adverse Events
FORM 18	End of Treatment
FORM 19	Details of Death
FORM 20	Consent Withdrawal
FORM 21	PI Declaration
QUESTIONNAIRES	Patient survey Nurse survey GP survey Pharmacist survey

8.4 Record Retention and Archiving

Upon completion of the study, data will be stored for a period of 10 years and securely destroyed after that period.

8.5 Compliance

The CI will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements including but not limited

- UK Policy Framework for Health and Social Care Research (2017)
- Medicines for Human Use (Clinical Trials) Regulations (2004)
- Medical Devices Regulations (EU MDR/IVDR 2017)

and SU policies and procedures and any subsequent amendments.

8.6 Research Governance Issues

8.6.1 Ethical Considerations

Permission to carry out this study will be given by an NHS Research Ethics Committee. Following approval, any subsequent amendments will be communicated to the Ethics Committee as well as the Sponsor, the investigators, the study participants, and the trial registry.

Participation in the study is voluntary. All those participating will receive a participant information sheet (PIS) and will need to sign a consent form indicating their understanding of their role in the study. The researcher will also be available to discuss with the participants any questions that they may have.

All participants will be given sufficient time to decide whether they wish to take part. They will be informed that their participation in voluntary and that they are free to withdraw at any time without giving a reason for doing so. Those participants agreeing to be interviewed will be informed that their anonymised data and quotes may be used in any relevant publications.

Service user participants or their representatives will be informed that if they chose to withdraw from the study, their medical care or legal rights will not be affected. They will also be informed that

- sections of their medical records may be looked at by individuals from Swansea University and from regulatory authorities
- the completed ADRe Profile will be shared with the study pharmacist, together with a copy of their medication record
- their GP will be informed of their participation and may review or adjust their prescribed medicines.

The research team will at all times use their judgement to identify any problems that may arise during the study. If they feel that improper or unprofessional behaviour is

being carried out relating to the study or in care delivery, then they can highlight the problem to the representative of the Sponsor of the ADRe Study, and R&D representative at Swansea Bay/Hywel Dda University Health Board.

If, at any time, the participant or their Consultee feels that abuse, malpractice or sub-optimal care is being carried out, then they will have the opportunity to speak to their GP surgery team, who will investigate further.

Declaration of interests: The chief investigator, principal investigator and all collaborators state they have no financial interests to declare in relation to the study.

8.7 Quality Control and Quality Assurance

8.7.1 Summary Monitoring Plan

A steering group committee will provide oversight of the progress and ensure delivery of the project outputs and achievement of the outcomes.

8.7.2 Audit and Inspection

Internal audits will be conducted by a sponsor's representative

8.8 Non-Compliance

Non-compliance may be captured from a variety of different sources including monitoring visits, CRFs, communications and updates. The sponsor will maintain a log of the non-compliances to ascertain if there are any trends developing which to be escalated. The sponsor will assess the non-compliances and action a timeframe in which they need to be dealt with. Each action will be given a different timeframe dependant on the severity. If the actions are not dealt with accordingly, the Research Governance Office will agree an appropriate action, including an on-site audit.

9. Trial Committees

A steering committee will provide oversight of the progress and ensure delivery of the project outputs and achievement of the outcomes.

10. Publication Policy

Only anonymized and de-identified data (or quotes from interviews) will be published or otherwise disseminated. This is also outlined in the Participant Information Sheet.

11. References

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12. Appendices

This section should contain the list (**Do not copy and paste the documents (denoted by underlining) as you do not want to make a substantial amendment every time that a substantial amendment is made for these documents**) of all pertinent documents that are associated with the management of the study.

The following is a list of attachments, those with an asterisk* must be submitted to the Research Ethics Committee with the protocol.

- Consent Form (versioned and dated appropriately)*
- Patient Information Sheet (versioned and dated appropriately)*
- GP letters/ advertisements/any other letters and documents to be given to the patient (versioned and dated appropriately)*
- An SAE/SUSAR reporting Organogram – who will be the study members (including BACK UP STAFF for ALL individuals) involved in the identification/reporting of the SAE
- Communication Plan Organogram – how will information be disseminated between the PI/CI and the members of the study team relating to the protocol and other trial related duties. This plan should ensure that there is always a physician (either PI/Sub-I) trained adequately on the study to ensure that a study trained medical physician is available to make any trial related decisions with regards to patient care, mainly with regards to adverse events or intercurrent illnesses.
- Source Data Identification List

Appendix

Appendix 1 – Information with regards to Safety Reporting in Non-CTIMP Research

	Who	When	How	To Whom
SAE	Chief Investigator	-Report to Sponsor within 24 hours of learning of the event -Report to the MREC within 15 days of learning of the event	SAE Report form for Non-CTIMPs, available from NRES website.	Sponsor and MREC
Urgent Safety Measures	Chief Investigator	Contact the Sponsor and MREC Immediately Within 3 days	By phone Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action.	Main REC and Sponsor Main REC with a copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt.
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion)	Annual Progress Report Form (non-CTIMPs) available from the NRES	Main REC

			website	
Declaration of the conclusion or early termination of the study	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination) *The end of study should be defined in the protocol*	End of Study Declaration form available from the NRES website	Main REC with a copy to be sent to the sponsor
Summary of final Report	Chief Investigator	Within one year of conclusion of the Research	No Standard Format However, the following Information should be included:- Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to participants	Main REC with a copy to be sent to the sponsor

Please outline the process/organisation within the study team to ensure that all SAE reporting is conducted in accordance with the sponsor's timelines. Display this information within an organogram to be located in the appendices in section 15 to ensure that there is a clear and distinct reporting process outlined with the study members detailed within this process.