At-Risk Registers Integrated into primary care to Stop Asthma crises in the UK (ARRISA-UK): A pragmatic cluster randomised trial with nested economic and process evaluations examining the effects of integrating at-risk asthma registers into primary care with internet-based training and support

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Research Ethics Reference	14/WA/1211

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1 Administrative information

This document was constructed using the Norwich Clinical Trials Unit (NCTU) Protocol template Version 2.0. It describes the At-Risk Registers Integrated into primary care to Stop Asthma crises in the UK (ARRISA-UK) trial, which is sponsored by University of East Anglia (UEA) and co-ordinated by NCTU.

It provides information about procedures for entering participants into the trial, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, trial population, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to registered investigators in the trial.

NCTU supports the commitment that its trials adhere to the SPIRIT guidelines. As such, the protocol template is based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement for protocols of clinical trials(1) and the Elaboration document(2), with reference to the consort statement on cluster randomised trials(3).

1.1 Compliance

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the Human Tissue (Quality and Safety for Human Application) Regulations 2007, the UK Data Protection Act, and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF). Agreements that include detailed roles and responsibilities will be in place between participating sites and NCTU.

Participating sites will inform NCTU by phone or email as soon as they are aware of a possible serious breach of compliance, so that NCTU can fulfil its requirement to report the breach if necessary within the timelines specified in the UK Clinical Trials Regulations (currently 7 days). The Chief Investigator (CI) and NCTU Director will assess whether or not the breach is 'serious'. For the purposes of this regulation a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the trial, or
- The scientific value of the trial.

1.2 Sponsor

UEA is the trial sponsor and has delegated responsibility for the overall management of the ARRISA-UK trial to NCTU including the delivery of the trial to time, target and budget.

1.3 Structured trial summary

Public Title	At-Risk Registers Integrated into primary care to Stop Asthma crises in the UK (ARRISA-UK)
Scientific Title	At-Risk Registers Integrated into primary care to Stop Asthma crises in the UK (ARRISA-UK): A pragmatic cluster randomised trial with nested economic and process evaluations examining the effects of integrating at-risk asthma registers into primary care with internet-based training and support
Primary Registry and Trial Identifying Number	ISRCTN 95472706
Source of Monetary or Material Support	National Institute for Health Research Health Technology Assessment Programme Grant number 13/34/70
Sponsor	University of East Anglia
Contact for Public Queries	Dr Stan Musgrave: ARRISA-UK.MED@uea.ac.uk
Contact for Scientific Queries	Dr Stan Musgrave: ARRISA-UK.MED@uea.ac.uk
Countries of Recruitment	UK
Health Condition(s) or Problem(s) Studied	Patients at a high risk of asthma related hospitalisations, A&E attendances or death
Intervention(s)	This is a complex intervention comprising the following four components 1) Establishment of register of at-risk patients 2) Practice-wide internet based training 3) Computerised Decision Support System: a computerised alert 4) Practice support: phone call and video reminders The intervention will target all healthcare professionals and reception staff within the whole practice with the objective of improving the care of patients with asthma who are at high risk of crisis events related to exacerbations of their disease.
Key Entry Criteria	**Inclusion criteria:** **Cluster** General Practitioner (GP) practices from the UK **Patients**: All patients registered with participating practices identified as having 'at-risk' asthma **Exclusion criteria:** **Cluster**: 1) practices already implementing a formal prospective process of flagging or otherwise targeting patients with at-risk asthma for the purpose of directing care to these individuals on a practice-wide basis 2) practices hosting or affected by research which might significantly influence the care of patients with 'at risk' asthma' **Patients**: Patient with recorded refusal for use of anonymous data in research, terminally ill patients and patients with COPD

Study Type	The study is a two-arm, cluster randomised, controlled multi-centre trial of a complex intervention of 262 GP practices involving 9170 patients with high-risk asthma integrating a mixed-methods process evaluation and economic evaluation. Randomisation will be performed centrally according to a computer-generated randomisation code with stratification for practice software and practice diploma trained nurse. Data will be captured anonymously by Clinical Practice Research Datalink (CPRD) and Secure Anonymised Information Linkage (SAIL) or a similar data extraction facility.
Date of First Enrolment	Anticipated as April 2015
Target Sample Size	262 practices with 9170 patients with high risk asthma
Primary Outcome(s)	The primary outcome is the difference in the proportion of at-risk patients (as identified by the initial search) who have an asthma-related crisis event (A&E attendance, hospitalisation or death) in the 12 months from the date the flags go live on the computer system in the intervention practices compared to the control group practices
Key Secondary Outcomes	Secondary outcomes: time to first crisis event, asthma control (as documented by "RCP 3 Questions in asthma"), prescribed asthma medications, attendance at appointments, medication adherence, smoking status, all cause admission and death, health care costs in all and "at-risk" asthma patients. Health economic analysis Routinely collected data from all asthma patients will enable detection of any impact (beneficial or adverse) on general asthma care in the practice. Routine data on processes of care, on-line information and questionnaires from practice staff completed before, during and after the training and after 12 months of the intervention, plus exit focus groups and interviews with stakeholders will contribute to the process evaluation and inform future wider implementation if shown to be beneficial.

1.4 Roles and responsibilities

1.4.1 Role of trial sponsor and funders

Name	Role
Norwich Medical School, University of East Anglia	Sponsor – overall responsibility for the conduct of the study
NIHR HTA	Funder – responsibility for trial design and funding
Norwich CTU	Responsibility for design, randomisation, data collection, analysis and dissemination within budget.

1.4.2 Trial Team

Name	Affiliation	Role and responsibilities
Prof Andrew Wilson	University of East Anglia	Chief Investigator
Dr Stanley Musgrave	NCTU	Clinical Trial Manager
Dr Erika Sims	NCTU	CTU Clinical Operations manager
Dr Allan Clark	University of East Anglia	Statistician
Prof Garry Barton	University of East Anglia	Health Economics
Mr Martin Pond	NCTU	Data Management
Dr Estelle Payerne	NCTU	Trial Assistant

1.4.3 Trial Management Group

Name	Affiliation	Role and responsibilities
Prof Andrew Wilson	University of East Anglia	Chief Investigator
Dr Stanley Musgrave	NCTU	Clinical Trial Manager
Dr Allan Clark	University of East Anglia	Statistician
Dr Jane Smith	University of Exeter	Process evaluation
Prof Garry Barton	University of East Anglia	Health Economist
Prof Hilary Pinnock	University of Edinburgh	Co-investigator
Prof Ann Louise Caress	University of Manchester	Co-investigator
Prof David Price	University of Aberdeen	Co-investigator
Prof Chris Griffiths	Barts and The London School of Medicine and Dentistry	Co-investigator
Prof Chris Butler	Oxford University	Co-investigator
Dr Mike Noble	Acle Medical Partnership	Co-investigator
Prof Ann-Marie Swart	University of East Anglia	Co-investigator
Prof Mike Thomas	University of Southampton	Co-investigator
Dr Samantha Walker	Asthma UK.	Co-investigator
Mr Michael Bang	Public and Patient Involvement Representative	
Ms Helen Paynter	Public and Patient Involvement Representative	

1.4.4 Trial Steering Committee

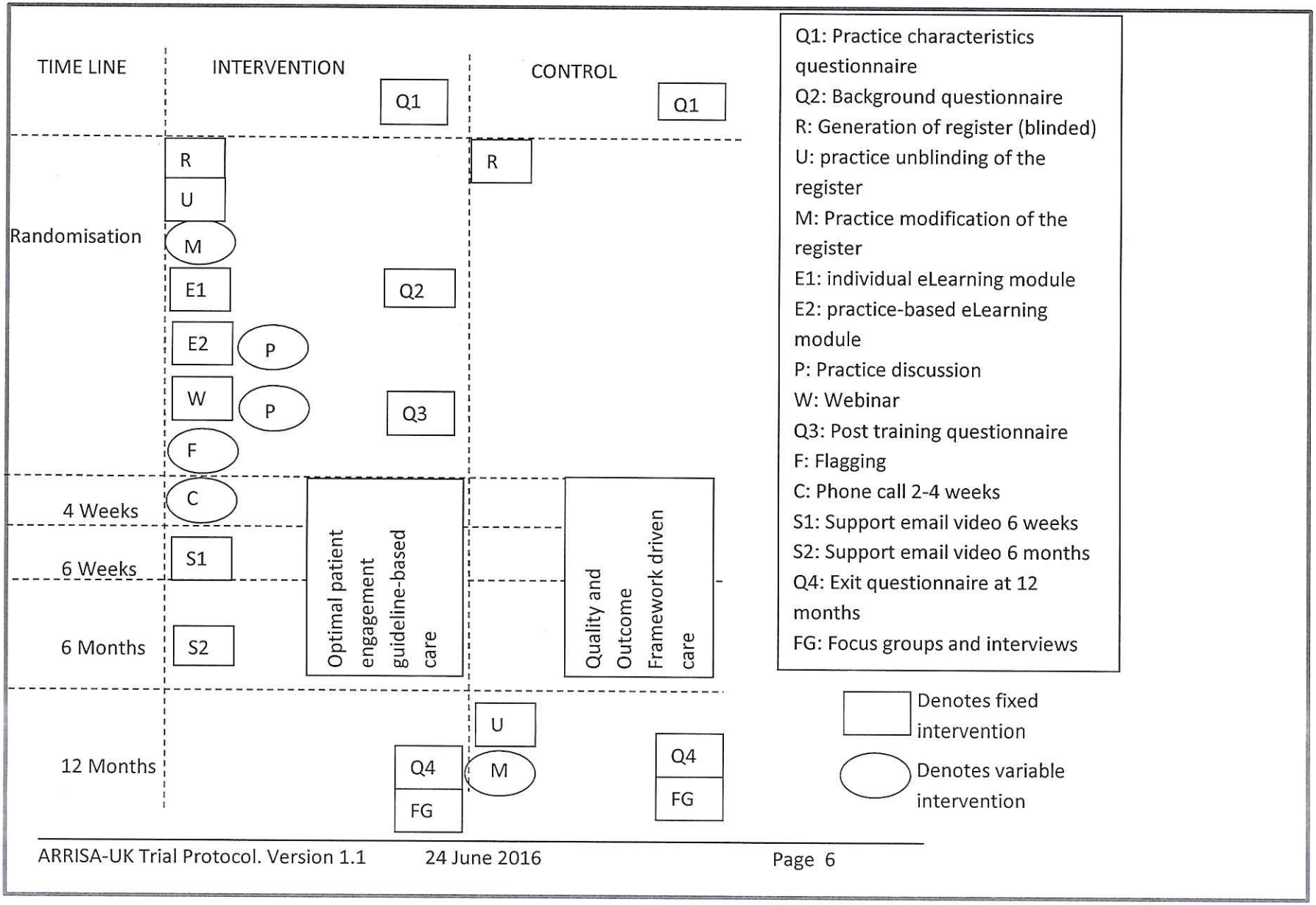
Name	Affiliation	Role and responsibilities
Dr Jennifer Quint	Imperial College London	Chair
Dr Richard Gilbert	Castle Partnership, Norwich	Expert member
Ms Stephanie Wolfe	Primary Research Ltd, Norwich	Expert Asthma Nurse

Mr David Weatherill	Public and Patient Involvement Representative
Mr David Bourn	Public and Patient Involvement Representative

1.4.5 Data Monitoring Committee

Name	Affiliation	Role and responsibilities
Prof Robbie Foy	University of Leeds	Chair
Dr Rachel Jordan	University of Birmingham	Expert member
Dr Jack Bowden	MRC Biostatistics Unit, Cambridge	Statistician

2 Trial Diagram



3 Abbreviations

AE	Adverse Event
AR	Adverse Reaction
BTS	British Thoracic Society
CCG	Clinical Commissioning Groups
CDSS	Computerised decision support systems
CI	Chief Investigator
CME	Continuing Medical Education
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
CRF	Case Report Form
CRN	Clinical research network
DSUR	Development Safety Update Report
EHR	Electronic Health Record
EQ5D	Euroqol 5-dimension questionnaire
EU	European Union
FEV1	Forced expiratory volume in 1 second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GP	General Practitioner
HES	Hospital episode statistics
ICH	International Conference on Harmonisation
ISRCTN	International Standard Randomised Controlled Trial Number
IT	Information Technology
ITT	Intention to Treat
MoU	Memorandum of Understanding
MRC	Medical Research Council
NCTU	Norwich Clinical Trials Unit
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NNUH	Norwich and Norfolk University Hospitals NHS Foundation Trust
NRAD	National Review of Asthma Deaths
ONS	Office of National Statistics
PI	Principal Investigator
PIS	Participant Information Sheet
PP	Per Protocol
QA	Quality Assurance
QALY	Quality Adjusted Life Years
QC	Quality Control
QOF	Quality and Outcomes Framework
R&D	Research and Development
REC	Research Ethics Committee
RGF	Research Governance Framework
SAE	Serious Adverse Event
SAIL	Secure Anonymised Information Linkage
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SSA	Site Specific Approval
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
ToR	Terms of Reference
TSC	Trial Steering Committee
UEA	University of East Anglia

4 Introduction

4.1 Background and Rationale

4.1.1 Asthma related crisis events

In the UK, which has one of the highest prevalence rates in Europe, there are 5.4 million patients with asthma, and asthma affects 1 in 5 households (AsthmaUK). A quarter of all asthma patients have poor asthma control(4) and each week in the UK, 22 patients die and 1400 are hospitalised due to asthma (Asthma UK). Acute deteriorations or "asthma attacks" result in major social, psychological and healthcare costs. For example, exacerbations are associated with doubling of the healthcare costs for managing severe asthma in both adults and children(5, 6). This is of great concern given that there are effective treatments and clear management guidelines for their use(7).

It is widely accepted that majority of deaths and hospital admissions are associated with preventable factors(8). This prompted the National Review of Asthma Deaths (www.rcplondon.ac.uk/nrad), which showed that poor access to care and poor adherence with medication were factors in the deaths of a larger proportion of patients. Systematic nationwide training and implementation programmes, mostly based in primary care, are able to reduce the morbidity and impact of asthma with reduced costs(9). Unfortunately, due to complicating clinical and psychosocial characteristics, patients with asthma who are at particular risk of exacerbations, often fail to engage in initiatives(10) such as self-management education that improve outcomes in general asthma populations(11) and are typically excluded from trials. Existing research evidence is thus unlikely to be generalisable to this group(12) and therefore research is urgently needed to identify better management strategies. The proposed intervention includes identification of at-risk patients with asthma, use of a computerised decision support system and wide training.

4.1.2 Risk stratification for asthma.

Confidential enquiries and case control studies have identified psychological or social factors as risks for asthma deaths and hospitalisations(13-16). Sixty per cent of patients with at-risk asthma defined according to current BTS guidelines(17, 18) have an exacerbation requiring prednisolone per year compared to 10% of the total asthma population (4). Creating 'at-risk' registers of patients requiring specialist or non-standard management and communicating this information is an important part of the care for patients within the NHS(19). Since 2006, the QOF has rewarded GP practices in the UK who keep a register of patients with terminal disease to improve the co-ordination of care for patients at the end of their lives (20) and British Thoracic Society (BTS) guidelines suggest at-risk registers may be useful for asthma(7).

4.1.3 Computerised decision support systems

Computerised decision support systems (CDSS) are information systems designed to improve decision-making and are increasingly employed within a modern NHS. Evidence suggests that the appropriateness of the trigger activating the CDSS, the ease of use and the helpfulness, simplicity and integration into routine care are important for integration(21, 22). The ARRISA CDSS is simple (a single flag), customised automatic (the flag will appear without any need for the clinician to activate the CDSS) timely (as the electronic record is opened) and inescapable (individual clinicians will not be

able to turn it off). Crucially, the CDSS will be supported by training for healthcare professionals and practice reception staff.

4.1.4 Practice based education/training

Continuing medical education (CME) is a fundamental aspect of Good Medical Practice(23) and aims to facilitate change in practice. Practice based education about clinical asthma guidelines with advice on the use of prompts to guide reviews has been shown to appropriately increase routine consultation rates (by 50%) and the recording of asthma related variables at consultations (by 4-66 times), and improve the prescribing of asthma related medication (by 43%)(24). In addition, a practice and patient-based intervention which included education and asthma nurse-led patient reviews with an emphasis on self-management plans improved asthma care, with an increase in the time to first attendance with acute asthma from 126 to 194 days (HR 0.73 (0.54-1)(25). Practice based interventions which utilise a practice champion (see below) from within the practice have been shown to be effective(25-27). Thus, practice based interventions are feasible and proactive engagement of patients improves patient outcomes.

4.1.5 At-Risk Registers in Severe Asthma

In a 'before and after' pilot study(28) involving 26 patients who had severe asthma, a previous hospitalisation for asthma or evidence of poor asthma control, electronic tagging of the patients EHRs with a flag and training all practice staff in appropriate actions to take on seeing the flag was associated with a reduction in the number of emergency events for asthma in these individuals. In a regional cluster randomised trial of 29 primary care practices in Norfolk(17) involving 911 patients with at-risk asthma defined according to BTS criteria, flagging of patients' EHR and a structured 1-hour practice-based training session led by the GP and nurse from the practice at which the pilot study was conducted did not reduce the primary composite endpoint of asthma exacerbations over one year defined according to current criteria(29, 30). However this masked reductions in hospitalisations (50 (95% CI 6 to 74) %) and accident and emergency attendances (26 (-31 to 58) %) and increases in the number of appropriate and timely prescriptions of prednisolone (31 (-8 to 85) %). The intervention was well received by practice staff (according to our exit questionnaire) and resulted in a cost saving of £138.21 (£1248 to -£910) per patient in the intervention arm.

4.1.6 Rationale for current study

Asthma is a common condition which results in a large number of unnecessary deaths and admissions in the UK every day. In addition the death rate has remained static over recent years and has not reduced. Our regional study shows that 'at-risk' registers may have potential as a strategy for reducing deaths and near fatal asthma: patients and their doctors need to know whether the results of the previous study will translate into a meaningful clinical benefit in a larger study. The current draft update of the BTS/SIGN British Asthma Guidelines includes a review of evidence on Organisation and Delivery of Care. It recommends further large scale studies are carried out to assess the impact of At-Risk Asthma Registers on unscheduled asthma care.

4.1.7 Explanation for choice of design

This intervention operates at the practice level. A cluster randomised trial design is therefore appropriate with the GP practice as the unit of randomisation. As such, although the majority of objectives (including primary endpoint) and the health economic analysis pertain to the participant level other objectives pertain to the cluster level as well (including the process evaluation). The study will be conducted in a controlled open study with blind assessment. The comparator will be standard usual care as defined by the current BTS/Scottish Intercollegiate Guideline Network British Asthma Guideline(18).

4.2 Aims and Objectives

The study aims to test the hypothesis that systematically identifying patients at risk of severe exacerbations of asthma, flagging their primary care EHR to provide enduring prompts at the time of all contacts with the practice, training all practice staff about the systematic management of these patients and providing on-going practice support (hereafter referred to as creation and integration of a primary care at-risk asthma register) will reduce crisis asthma events (asthma related deaths, hospitalisations and A&E attendances) and be clinically acceptable and cost effective without detriment to the care of non-at-risk asthma patients

4.2.1 Primary Objective

To determine whether the creation and integration of an at-risk register in primary care for patients with at-risk asthma, decreases the percentage of patients at-risk of an asthma-related (defined as asthma, mixed asthma/COPD and/or mixed asthma/respiratory infections) crisis event (hospitalisation, accident and emergency attendance or death) over 12 months from activation of the flags compared to control practices.

4.2.2 Secondary objectives

To determine whether the creation and integration of an at-risk register in primary care for patients with asthma:

1. increases the time to first asthma related crisis event (defined as above) for at-risk patients
2. affects the care of all patients with asthma (including those not on the register) in terms of the proportion of all patients with a crisis event (defined above) and/or the time to first, crisis event.
3. improves asthma control as assessed by standard morbidity questions, the "RCP 3 questions for asthma", which are advocated by QOF (Difficulty sleeping, daytime symptoms, interference with usual activities) for all patients with asthma
4. reduces all cause admissions and death for all patients with asthma
5. improves processes of care for all patients with asthma

4.2.3 Health economic objective

To determine whether the creation and integration of an at-risk register in primary care for patients with asthma is cost effective

4.2.4 Process evaluation objective

(1) To determine whether the creation and integration of an at-risk register in primary care is perceived as acceptable and useful to healthcare professionals and patients, (2) to identify characteristics that influence uptake, integration and effectiveness of the intervention and its likely sustainability in practice, and (3) explore causal mechanisms leading to changes in outcomes (e.g. via

effects on intermediary outcomes such as practice procedures, staff behaviours and awareness, processes of care), including any unanticipated effects.

4.2.5 Safety

There will be no documentation or reporting of non-serious adverse events. Deaths and hospitalisation are the primary effectiveness outcome and will not be reported as safety measures. Practices will be asked to capture complaints or important study related adverse events by completing a complaints/adverse events form and forward to NCTU.

5 Trial Design

This is a two-arm multicentre cluster randomised controlled pragmatic trial plus health economic and process evaluation of a complex intervention comprising:

1) creating an asthma at-risk register
2) practice training
3) computerised decision support system (CDSS)
4) practice support.

The intervention will target all healthcare professionals and reception staff within the intervention practices with the objective of improving the care of patients with asthma who are at high risk of crisis events related to exacerbations of their disease (Figure 1). The setting will be primary care practices within the United Kingdom which will be identified mainly via clinical research networks and selected by purposive sampling as discussed below. The unit of randomisation will be GP practices. Randomisation of GP practices will be performed centrally according to a computer generated randomisation code.

A practice demographic questionnaire will be completed by all practice as part of the recruitment process before randomisation. Data on outcomes and processes of care will be captured anonymously by Clinical Practice Research Datalink (CPRD) or equivalent and Secure Anonymised Information Linkage (SAIL). A representative of each practice staff discipline (see below) will be asked to undertake training which comprises part of the intervention (see below). These individuals will be asked questions as part of the training to capture information about their understanding and awareness of at-risk asthma their roles in managing asthma patients, their confidence in taking appropriate action when in contact with an at-risk asthma patient and opinions about the training. Data regarding the resource use required to complete the training will be captured. At the end of the study practice representatives (see below) will asked how their practice has changed and their opinions about the intervention. Control practices will be asked whether there has been any major change to their practice policies regarding asthma management over the preceding 12 months. Towards the end of the study up to 27 focus groups and 15 individual interviews will be undertaken with practice staff and patients including those from the whole asthma population and those with at-risk asthma in the intervention and control groups. Participants in focus groups and interviews will provide written informed consent before being involved.

6 Participants

6.1 Clusters – Primary Care Practices

6.1.1 Practice Selection

Primary care practices will be identified by the Primary Care theme of the Local Clinical Research Networks (CRN). Practices will not be required to have previously entered an agreement with CPRD prior to enrolment in this study but will be required to agree for data to be captured anonymously by CPRD, SAIL or an equivalent. This will be aided by a regional recruitment questionnaire (to capture data regarding practice demographics, practice staff (in particular the role and training of the asthma nurse), methods for managing all and at-risk patients with asthma, competing studies etc.), data which will be also used to assess generalisability. Practices will be enrolled initially from a few regions (Cardiff, Edinburgh, Kent, London, Manchester, Norfolk/Suffolk, Southampton/Exeter), and recruitment will be overseen by the regional leads (or deputies) who are co-investigators on this application. Extension to other regions will occur depending on recruitment rates.

6.1.2 Site approval and activation

Contracts will be between University of East Anglia and Clinical Commissioning Groups (CCG) or individual practices as required

6.1.3 Inclusion criteria

General practices in the UK

6.1.4 Exclusion criteria

1) Practices already implementing a formal prospective process of identification of patients with at-risk asthma and practice wide targeting of asthma care on every approach to patient or their record.

2) Practices hosting or affected by research which might significantly influence the practice wide process of care of patients with 'at risk' asthma.

6.2 Individual participants – patients with asthma

6.2.1 Inclusion criteria

6.2.1.1 Intervention

1) Patients identified as having at-risk asthma from an algorithm via routinely collected data

6.2.1.2 Evaluation

1) All patients with asthma

2) Practice staff*

3) *FOR PROCESS EVALUATION AND HEALTH ECONOMIC ANALYSIS ONLY

6.2.2 Exclusion criteria

1) Patients with recorded refusal for use of anonymous data in research

2) Terminally ill patients receiving palliative care only

3) Patients less than 16 years of age and unable to communicate in English*

*FOR FOCUS GROUPS AND INTERVIEWS ONLY

7 Interventions

7.1 Interventional Practices

This is a practice wide complex intervention comprising four components. Full details of the intervention are available in the study training manual. The intervention pertains to the cluster level.

7.1.1 Establishment of register:

We have developed and validated an algorithm for identifying those patients most at risk of being admitted to hospital or dying from an asthma exacerbation from routinely collected primary care data including previous exacerbation history, coding for anxiety or depression, smoking history and prescribing data and laboratory results. Automated electronic searches will be used to identify patients with at risk-asthma from practice-based data based on this algorithm. This will be a two stage process with initial generation of a blind list then code to provide the names and details of the patients. Programmes and instructions, with frequently asked questions, for the specific computer software programme of the practice will be sent to the information technology (IT) lead by email or CD.

The asthma GP lead at each intervention practice will receive by email a 1 page document defining "at-risk asthma". GPs and asthma nurses will be welcome to review the computer generated list against the definition, delete any who should not be on the list and identify any other 'at-risk' patients known to them provided justification for this change is documented. For the duration of the study the practice champion (see below) will be permitted to add "at-risk" patients who join the practice and, in exceptional circumstances, remove patients in whom enrolment in the study inappropriate e.g. receiving palliative care only although for the purposes of our analyses the register will remain unchanged.

7.1.2 Practice-wide, internet-based training

This will be an innovative multi-component practice-wide intervention based on the training developed for the regional ARRISA(17) study but incorporating eLearning modules that have been previously validated and shown to be successful in changing clinician behaviour(31). Each practice will be asked to nominate a representative from each staff discipline e.g. nurse, GP, receptionist, pharmacist (in dispensing practices), manager etc. (referred to hereafter as practice representatives). A dedicated member of the practice staff (generally the practice asthma nurse) will be charged with championing the intervention at the practice and ensuring dissemination via the staff representatives to maximise uptake. This individual will be referred to as the practice-champion. Discipline-specific summary documentation will be emailed to each practice representative. These documents will be one page of A4, describing the rationale for the study, details of the training programme and providing log in details to the web-based training resource. The main purpose of the education is to advise all practice staff on actions to take when presented with the electronic flag on the EHRs of an at-risk patient.

Practice representatives will be requested to complete password protected web-based eLearning modules based on the material delivered via face-to-face contact in the regional ARRISA trial. The eLearning modules will be developed in conjunction with Healthcare-Learning (www.healthcare-learning.com) who have experience in delivering eLearning tools including the STAR educational programme (www.stemmingthetide.org). It will be hosted on the HealthCare Learning secure website with links from the Asthma UK Centre for Applied Research website and comprise:

A) An individually completed module. This will provide training with information about the national and patient perspective of managing at-risk asthma, NRAD results (www.rcplondon.ac.uk/nrad), findings from the ARRISA studies(17, 28), the flagging tools and discipline specific training as to the action to be undertaken on seeing the flag. Data from the self-assessments used as part of the e-Learning package, and statistics captured by the software on timing and frequency of access by individual staff etc. will also feed into aspects of the process evaluation. This module will take up to 45 minutes to complete

B) A practice-staff representative completed module which is organised and chaired by the practice-based champion. The purpose of this module is to permit the practice staff to collectively reflect on the material contained in the first module and encourage the practice staff to agree and document how the intervention will be implemented in the practice. This includes the wording of the flag, proposed actions of each staff discipline, practice dissemination plan, stance on informing patients about at-risk status, method for communicating with out of hours service. This module will take up to 45 minutes to complete

C) A webinar
Ideally within 8 weeks of completion of this module, the practice representatives will be asked to dial into a 30 minute "webinar" (online seminar discussion) which will review the learning objectives and outcome from the modules. It will permit discussion within and between practices (in groups of between 2 and 8) participating in the study, allow them to share experiences and ideas, and refine their practice integration and dissemination plans accordingly.

Training will be accredited and approved for continuing medical education (CME).

7.1.3 Computerised Decision Support System

The CDSS will consist of a flag which appears on the EHR whenever a patient on the at-risk asthma register makes any contact with any member of the practice team. The type of flag available is dependent on the software used to manage the practice's EHRs and varies between pop-ups that actively need clearing from screen to yellow post-it style notes remaining on screen. The practice staff will not have the opportunity to switch the flagging off. The wording of the flag will have been chosen by the practice during the second module but must be no less than 20 and no more than 40 characters. Instructions for generating the flag will be provided to the practice manager/IT lead. The flagging will go live after the completion of the minimum training as defined in section 7.3.

7.1.4 Practice support:

The practice champion will receive a phone call at 4 weeks (between 2 and 6 weeks) after the start of the intervention to ensure that there are no technical or other fundamental process issues. This will be undertaken by an unblinded nurse researcher with clinical experience of asthma. Practice staff will receive emails containing links to reminder videos at 6 weeks and 6 months. Both of these reminder videos will be 60-90 seconds long. They will remind practices of the national statistics on asthma events and the importance of targeting, engaging with and managing patients with at-risk asthma.

There will be study newsletters circulated every 3 months for the duration of the study. They will provide updates of the study progress including number of recruited sites, timelines etc.

Practice staff will have access to a helpline manned by an un-blinded IT technician for help with technical issues regarding the software for the duration of the study. A website will contain links to national guidelines and a frequently asked questions section.

7.2 Control practices

Control practices will produce a list of patients who meet the definition of at-risk asthma from the algorithm. However the names and details of the patients will be blind to the practice staff and they will be given the code to permit patient identification at the conclusion of the study i.e. after the assessments have been made. In addition, after the completion of the study, practice staff will be permitted to modify the register in the same manner as for intervention practices (at the beginning of the study)

The control practices will continue to provide their standard usual care. This is likely to vary between practices, but should reflect the recommendations of the British Thoracic Society/Scottish Intercollegiate Guideline Network British Asthma Guideline(18). Primary care practices are incentivised to provide care to BTS/SIGN standards as defined by the Quality and Outcome Framework(32). This recommends creating a register of all patients with asthma and offering at least annual practice-based asthma reviews (typically in nurse-led clinics), Recognised management includes checking asthma control with the RCP3 questions, checking smoking status and offering cessation advice, assessing/teaching inhaler technique, assessing and offering advice on adherence, and delivering patient self-management education which may include provision of action plans and self-monitoring tools(33). Follow-up in secondary care outpatient clinics and use of emergency primary and secondary care will be available as usual for patients if required.

7.3 Compliance and Adherence

Compliance with the training will be ensured as the flag will only be activated after the completion of minimum training. The definition of minimum training is at least one practice member completing both e-learning training modules. Assessment of compliance with the intervention will form part of the process evaluation and will include examination of modifications to the register, uptake of the training and engagement with the follow-up phone calls.

8 Outcomes

8.1 Primary Outcomes

The percentage of at-risk patients with an asthma-related (defined as asthma, mixed asthma/COPD and/or mixed asthma/respiratory infections) crisis event (hospitalisation, accident and emergency attendance or death) over 12 months from activation of the flags

8.2 Secondary Outcomes

1. The time to first asthma related crisis event (defined as above) for at-risk patients
2. The percentage of all patients with an asthma related crisis event (as above) and the time to first of these events.
3. The percentage of all asthma patients with good control – answering no to all of the "RCP 3 questions for asthma" (Difficulty sleeping, daytime symptoms, interference with usual activities)
4. The percentage of all patients with asthma with a hospital admission or death for any reason

5. The number of the following (per patient per year) for both at-risk asthma patients and all asthma patients:
    a. short acting bronchodilator prescriptions issued
    b. prescriptions of systemic corticosteroids for asthma exacerbations and antibiotic treated lower respiratory tract infections
    c. modifications of the prescription of asthma related medications to align more closely with current guidelines (e.g. increased use of inhaled corticosteroids)
    d. written personalised asthma action plans and patient self-monitoring with peak flow diaries
    e. inhaler technique assessments recorded
    f. smoking cessation advice or smoking cessation medications
    g. flu vaccinations

    The rate of the following (per patient per year)

    h. "did not attend" at primary and secondary care routine appointments
    i. adherence to medication determined from validated computer based calculations from prescription data

8.3 Health economic outcome

The main outcome measure in the economic analysis will be based on the primary outcome for the study. The number of asthma related crisis event will be estimated for both study arms. The incremental effect will be the estimated mean difference (between arms) in number of asthma crisis events, after taking account of clustering.

8.4 Process evaluation outcomes

The outcomes include quantitative and qualitative assessments of the views of healthcare professionals and patients, practice procedures and processes of care, staff behaviours and awareness, and indicators of intervention uptake, implementation and compliance. The process evaluation will also explore how key intermediary and primary and secondary outcomes (e.g. asthma control) are affected by contextual characteristics (e.g. practice characteristics), including identification of factors that will improve effectiveness and sustainability in practice.

8.5 Trial Closure

The end of the trial will be defined as 36 months following randomisation of the last practice.

8.6 Recruitment and Retention

8.6.1 Recruitment - practices

Primary care practices will be identified by the Primary Care theme of the Local Clinical Research Networks (CRN) and also with assistance from CPRD or equivalent and SAIL from 6 regions initially as described above.

8.6.2 Recruitment – patients

Patients will not be recruited into the main study. They will be identified by the algorithm, provided with the clinical service by participating practices, and their anonymous data used without enrolment or consent. For the qualitative sub study, patients will be identified and recruited by practice staff.

8.6.3 Retention – practices

The study is designed so that data is captured remotely by CPRD, SAIL or equivalent without the involvement of the GP practice. The Read code that the flag is based on cannot be removed by the practice (though the protocol which makes the flag display can be disabled if a practice withdraws). We will ensure engagement with completion of the training module as the flag will not be activated unless minimal training has occurred. We will send reminders to all of the practice representatives by email on two occasions then by phone to encourage engagement with the training.

8.6.4 Retention – patients

The practice champion may modify the register but the analysis will be conducted using data from all patients on the original register without additions or withdrawals. Patients have the right to refuse access to their data at any point until the conclusion of the data extraction. The data for the primary endpoint will be captured for patients who leave a practice via Hospital Episode Statistics (HES) and Office of National Statistics (ONS).

9 Assignment of Intervention

9.1 Allocation

9.1.1 Sequence generation

The randomisation code for allocating each practice to the intervention or control arms of the study will be generated via computer written code using minimisation. Minimisation will be performed for i) practice software (Vision/EMIs/SystmOne+others) and ii) practice asthma diploma trained nurse (yes/no) at randomisation.

9.1.2 Allocation Implementation

Practices will be allocated to the intervention or control group by a process embedded in the web-based data Management system. The randomisation code will be saved in the study database for later decoding. An email will be sent to practice manager and practice champion informing them whether they have been randomised to the intervention or control arms of the study with appropriate log in details for the study websites and, for the intervention practice, the eLearning modules.

9.2 Blinding

The study will be conducted in a controlled open study with blind assessment. The practices (clusters) cannot be blind to the intervention. The patients with asthma may or not be blind to the intervention depending on individual practice decision/policy. As far as possible, those researchers not interacting with the sites implementing the intervention will remain blind throughout the study and analysis. The statistical analysis team will be blind to the intervention throughout. The health economists will be blind during their initial determination of costs and until that point in the analysis plan where they must include costs associated with the allocation. The researchers implementing the intervention, including the physician leading the webinar training programme, the qualitative interview and focus group researchers, and the research trial staff providing assistance on practice sign up, follow up phone calls and providing support for the software, will be aware of allocation.

10 Data Collection, Management and Analysis

10.1 Data Collection Methods

10.1.1 Quantitative data

Initial feasibility questionnaire sent out to all practices, which will include basic practice characteristics that will be examined in later analyses as contextual factors potentially influencing integration into practice and effectiveness.

Intervention practices will be asked to identify ARRISA-UK practice champions (above) and control practices will be asked to identify an individual for the purpose of contact with NCTU.

All practices must be prepared to share their practice EHRs with CPRD, SAIL or another organisation specialised in primary care data extraction. Obtaining data in this way not only permits linkage to different databases (practice EHRs, ONS, HES) but permits data capture without burdening the practice or patients. This will be enhanced by the addition of central mortality data (date and causes of death) as well as certain key data from Hospital Episode Statistics (HES). All practices (control and intervention) will be asked to insert a specific Read code into the EHRs of at-risk asthma patients to denote participation in this study. This will be used by data managers and statisticians to identify these patients and distinguish their data from all patients with active asthma in the practice. For the purposes of data collection active asthma will be defined using the QOF criterion: (32) Read codes for asthma diagnosis plus asthma therapy in the past 2 years, excluding those coded as asthma resolved but not excluding QOF exception codes. After twelve months, data extractions will be provided for all patients with asthma in the practice containing data for the year before and the year after the beginning of the intervention for clinical event data and the last recorded value for demographic and patients characterisation data (weight, height, smoking status etc.).

Data will be captured from the training website for the purpose of process evaluation. This includes completion rates, time taken to undertake the training, time that the training took place and changes in knowledge, attitudes and motivation following the training by reviewing the self-assessment answers. The number of hits on the website resource pages (e.g. frequently asked questions) will be counted. Likewise, data collected from the helplines and the phone call between 2-6 weeks will capture details of problems with the intervention and practice engagement. Practice staff will be asked to complete their implementation and dissemination plans, and these will be captured along with notes from the webinar facilitator to assess details of practice-level dissemination and implementation of the intervention. The IT lead will be asked to provide details of how long it took to produce the list of at-risk asthma patients and then provide the names and details of the patients.

After the training, all of the practice staff representatives from intervention practices will also be asked to complete a questionnaire to provide feedback regarding the training and whether they attended the group training and for how long. This will supplement the data captured by the training software and assess the acceptability of the intervention as well as any changes in knowledge, attitudes and motivation etc. over time as a result of the training and experience with using the alerts. At the end of the study all practice representatives from the intervention practices will be

asked to complete questionnaires to provide information regarding their experience of the intervention. The ARRISA-UK practice champion from the intervention practice and the practice contact from the control practice will be asked questions about major changes in practice asthma management policies over preceding 12 months. Informed by findings from analyses of preliminary process data, focus groups and interviews, comprising all relevant stakeholders including patients and practice staff, will be conducted to explore any additional mechanisms or unintended consequences of the intervention that had not been anticipated, the acceptability of the intervention and additional factors important for implementation (See 10.1.2). Information from the focus groups may inform data that requires to be captured quantitatively in order to fully understand the intervention, its consequences and it integration into routine practice.

10.1.2 Qualitative data

Staff and patient focus groups and interviews will be undertaken towards the end of the study to explore perceived benefits and disbenefits, unanticipated consequences, experiences of the intervention and any additional issues related to implementation, causal mechanisms and contextual factors influencing these, guided by prior analyses of quantitative process evaluation data. Dual moderator focus groups(34), will be undertaken with at least six practice/staff group teams (approx. eight participants/group) across each of three study regions. A maximum diversity sample of participants will be recruited to reflect a range of engagement with the intervention/training and practice and staff characteristics, guided by quantitative data if this identifies issues for particular staff groups or types of practice. Each focus group will last approximately one hour and will be audio recorded, then transcribed verbatim. A further three focus groups, using the same methodology as above, will be undertaken with patients from three of the practices above. The purpose of these will be to explore patients' experiences and perspectives on the strengths and limitations of 'at risk' registers and their potential for impact on patients' asthma management. The number of focus groups and interviews will be less than these estimates if data saturation becomes apparent. Up to 15 individual interviews will be conducted on the assumption that the prior process data arising from the quantitative data collection or early focus groups reveals issues that need more in-depth exploration.

10.2 Data Management

Anonymised data will be received from CPRD, SAIL or another organisation specialised in primary care data extraction and the eLearning module database. It will be uploaded onto the central database stored on the servers based at UEA. The database will be password protected and only accessible to members of the ARRISA-UK trial team at NCTU and external regulators. The server is in a secure room, which is protected by CCTV, where access is restricted to members of the UEA Information Systems team by security door access. The study database will be built using Microsoft SQL Server tools and all internet traffic will be encrypted using the standard SSL (Secure Sockets Layer) methodology. Periodically and at database lock the data will be validated for errors and inconsistencies. The database is designed to comply with the principles of ICH Good Clinical Practice (GCP), within the Standard Operating Procedures for Data Management in NCTU and also where appropriate with UEA IT procedures. The database and coding values have been developed by the Head of Data Management in conjunction with the study statistician and other NCTU members. After completion of the trial the database will be retained on the servers of UEA for 15 years for on-going analysis of secondary outcomes.

10.3 Analysis

10.3.1 Sample Size

A total sample size of 8204 patients from 235 practices will provide 90% power to detect a difference in the primary outcome from 7% to 5% (effect size of 0.3) assuming a cluster size of 35 and intraclass correlation of 0.01. These estimates are from the event rate and prevalence of the predicted hospitalisations and A&E attendance, as a whole and per practice, obtained from a database of 48,000 patients used to generate the new at-risk algorithm. Patients will only be removed from the register in exceptional circumstances and we estimate that less than 10% of patients will leave their practice(35). We will therefore recruit a total of 9170 patients with at-risk asthma from 262 practices. The average cluster size has been estimated from Clinical Research Networks (CRN) data however if this assumption is incorrect the sample size will be increased accordingly up to a maximum of 10000 patients. If more than 10% of practices do not undergo minimum training and flagging, additional practices will be recruited. A decision to stop the study will be considered if the power of the study is reduced to less than 80% or when more than 30% of practices fail to undergo training to a minimal degree and/or do not activate the flag.

10.3.2 Analysis Plans

Detailed statistical, health economic and process evaluation plans will be produced and agreed with both the TSC and DMC prior to the analysis of any data.

10.3.4 Methods – Outcomes

Please see section 8

10.3.5 Effectiveness Analyses

The primary comparison of treatment arms will be based on the intention-to-treat principle including all patients identified with "at risk" asthma as identified by the risk algorithm. The primary outcome will be analysed on an individual-level using a logistic regression model with a random effect to allow for the clustering of patients by practice and fixed effects for the factors included in the stratification, i.e. practice software and practice diploma trained nurse. A similar model will be used for the number of events, based on a Poisson regression model with random and fixed effects, and the time until the first event. Secondary outcomes will be analysed in a similar fashion, which is to say that the binary outcomes will be analysed using logistic regression models and all count outcomes using Poisson regression. All model assumptions will be assessed using appropriate techniques and for Poisson regression models over dispersion will also be checked.

10.3.6 Additional Analyses – Subgroup

As well as the above intention-to-treat analyses (of data from patients on the register at the time of randomisation) some further exploratory analyses will be conducted. In particular a) restriction of the analyses to only those patients who remain on the register over the course of the year (unless this is due to death); b) restriction of the analysis to those intervention practices where all staff representatives completed over 80% of the training; c) inclusion of those individuals subsequently added to the "at risk" register by the practice.

10.3.7 Health economic Analyses

An economic evaluation will be conducted alongside the trial. Costs will be estimated from the viewpoint of the NHS. Resources associated with the creation and integration of the at-risk register

for patients with asthma will be collected (this will include time spent searching for and identifying patients, setting up flags, training and setting up other associated support e.g. web-based material and practice follow-up). Additionally, details of other NHS resource use will be extracted from routinely recorded data, where this will include contacts with health professionals, medication and hospital admissions. Appropriate unit costs e.g. Curtis (2012) will subsequently be assigned to each item of resource use for a standard price year. The incremental cost of the at-risk register compared with standard NHS care without an at-risk register, over the 12 month trial period, will then be estimated by comparing the mean cost in each arm of the study (with adjustment for clustering).

The main outcome measure in the economic analysis will be the primary outcome for the study i.e. the level of asthma related crisis events will be estimated for both study arms. The incremental effect will be the estimated mean difference (between arms) in number of asthma crisis events, after taking account of clustering.

The above analyses will enable both the incremental cost and incremental effect associated with the at-risk register to be estimated. The associated level of uncertainty will also be characterised by estimating cost-effectiveness acceptability curves. Sensitivity analysis will also be undertaken to assess the robustness of conclusions to changes in key assumptions. In line with the outcome analysis all analysis will be conducted on an intention-to-treat basis.

10.3.8 Process evaluation Analyses

A comprehensive, mixed-methods process evaluation in line with the forthcoming Medical Research Council guidance and a recently published framework on the conduct of process evaluation alongside cluster trials(36) will be undertaken. The process evaluation will adopt a mixed-methods sequential explanatory approach(37) whereby descriptive summaries of initial quantitative data will inform the focus of later qualitative research, and any novel findings from the qualitative research will generate further hypotheses for exploration with analyses of quantitative data where possible. The influence of contextual factors (e.g. practice characteristics) on intermediary (e.g. process of care) and clinical outcomes (e.g. asthma control) will be explored using regression models.

10.3.9 Qualitative Analyses

Analyses of focus groups and interviews will be undertaken using Framework Analysis(38) and supported by use of NVivo 9.0 software. At least two project team members will analyse each transcript, to enhance rigour.

10.4 Data Monitoring

10.4.1 Data Monitoring Committee

Details of the roles and responsibilities of the Data Monitoring Committee (DMC), including membership, relationships with other committees, decision making processes, and the timing and frequency of interim analyses (and description of stopping rules and/or guidelines where applicable) are described in detail in the ARRISA-UK DMC Terms of Reference (ToR).

10.4.2 Interim Analyses

There is no plan for an interim analysis of ARRISA-UK data.

10.4.3 Data Monitoring for Harm

Data capture will occur after the conclusion of the 12 month follow-up period. A descriptive analysis of adverse events will be undertaken at the end of the study. No formal on-going review of safety data is planned during the study. Complaints or study related adverse events will be detailed and described.

11 Quality Assurance and Control

11.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the ARRISA-UK trial are based on the standard NCTU Quality Management Policy that includes a formal Risk Assessment, and that acknowledges the risks associated with the conduct of the trial and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on the rights and safety of participants; project concept including trial design, reliability of results and institutional risk; project management; and other considerations.

QA is defined as all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC is defined as the operational techniques and activities performed within the QA system to verify that the requirements for quality of the trial related activities are fulfilled.

11.2 Monitoring

There will be no study monitoring other than recruitment rates and cluster size in order to review the assumptions used to power calculation if required.

11.3 Trial Oversight

Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harms; completeness, accuracy and timeliness of data collection; and will verify adherence to applicable policies detailed in the Compliance section of the protocol. Independent trial oversight complies with the NCTU trial oversight policy.

11.3.1 Trial Management Team

The Trial Management Team (TMT) will be set up to assist with developing the design, co-ordination and day to day operational issues in the management of the trial, including budget management. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMT terms of reference.

11.3.2 Trial Management Group

A Trial Management Group (TMG) will be set up to assist with developing the design, co-ordination and strategic management of the trial. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMG terms of reference.

11.3.3 Trial Steering Committee

The Trial Steering Committee (TSC) is the independent group responsible for oversight of the trial in order to safeguard the interests of trial participants. The TSC provides advice to the CI, NCTU, the funder and sponsor on all aspects of the trial through its independent Chair. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TSC terms of reference.

11.3.4 Data Monitoring Committee

The Data Monitoring Committee (DMC) is the only oversight body that has access to unblinded data. The DMC is responsible for safeguarding the interests of trial participants, monitoring the accumulating data and making recommendations to the TSC on whether the trial should continue as planned.

11.3.5 Trial Sponsor

The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage and finance the trial. UEA is the trial sponsor. Formal agreements are in place for sponsor's activities that are delegated to the NCTU.

12 Ethics and Dissemination

12.1 Research Ethics Approval

Before initiation of the trial at any clinical site, the protocol, all informed consent forms and any material to be given to the prospective participants will be submitted to the relevant REC for approval. Any subsequent amendments to these documents will be submitted for further approval.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected.

12.2 Other Approvals

The protocol will be submitted to the relevant R&D department of each participating practice. A copy of the local R&D approval must be forwarded to the co-ordinating centre before sites are enrolled into the trial.

The protocol has received formal approval and methodological, statistical, clinical and operational input from the NCTU Protocol Review Committee.

12.3 Protocol Amendments

Substantial protocol amendments will be co-ordinated by the ARRISA-UK trial team at NCTU after approval by the TSC. Investigators and other relevant parties will be notified of amendments in a timely manner so as to ensure appropriate regulatory and ethical principles are met. A request for confirmation of receipt from sites will be made. A summary of protocol amendments will be maintained within the protocol itself.

12.4 Consent or Assent

Practices managers will be asked to sign a contract with UEA on behalf of all practice staff. Patients will not be required to be asked to provide consent to use their data. This meets ethical standards for the following reasons:

a) The intervention is at practice level and it is the practice staff/infrastructure that are directly involved, not the patients. The investigation is of a process of care to support best practice not a novel intervention on patients.

b) Using anonymous patient data in this way is a recognised strategy to improve patient care in line with the government agenda including the care.data initiative (http://www.england.nhs.uk/ourwork/tsd/care-data/).

c) The extracted data are completely anonymised. Asthma is a common condition and therefore patients are not potentially identifiable. The Read code identifying those patients are at-risk remains on the practice systems and only non-identifiable data will be extracted. The data extraction methods meet all legal requirements (http://www.cprd.com/governance/)

d) The study follows accepted practice:

1) It was felt that written informed consent from patients for similar studies using anonymous population level data(17, 31, 35, 39) was not required after ethical review.

2) All practices will inform patients (e.g. by displaying a poster, statements on web-sites) that their data may be used anonymously for research. This is standard procedure in research-ready practices. Written informed consent will be obtained from patients to participate in focus groups or interviews.

12.5 Confidentiality

The extracted data are completely anonymised. Asthma is a common condition and therefore patients are not potentially identifiable. The Read code identifying those patients are at-risk remains on the practice systems and only non-identifiable data will be extracted. Quotes from patients at focus groups or interviews that are published will be anonymised.

12.6 Other ethical issues

The focus group and interviews will not be exploring highly sensitive issues and therefore the study has no material ethical issues. Other than the focus groups and interviews, all data will be captured anonymously from routinely captured sources.

12.7 Declaration of Interests

The investigators named on the protocol have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the trial.

12.8 Indemnity

UEA holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UEA has been negligent. UEA does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or not. This does not affect the participant's right to seek compensation via the non-negligence route.

12.9 Finance

The ARRISA-UK trial is fully funded by National Institute for Health Research Health Technology Assessment Grant number 13/34/70.

12.10 Archiving

The investigators agree to archive and/or arrange for secure, password protected storage of ARRISA-UK trial materials and records for periods corresponding to the type of material.

- Personal identifiable information which is solely the identification and contact details of those consenting for the focus groups and interviews in the trial (held securely and the Exeter and Manchester researcher facilities) will be held for 12 months.
- The electronic files of anonymised transcripts and files used in the analysis of qualitative data will be held at NCTU for 15 years.
- The anonymised routine practice data will be held at the NCTU for a minimum of 15 years after the close of the trial unless otherwise advised by the TSC.
- In all cases at the end of the archive period the data will be securely destroyed.

12.11 Access to Data

Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the TMG and TSC. Considerations for approving access are documented in the TMG and TSC Terms of Reference.

12.12 Ancillary and Post-trial Care

At the end of the study the control practices will be offered the intervention if it is deemed clinically beneficial in terms of the primary outcome. The summary of the findings will be posted on the ARRISA-UK website and the website will remain live if the intervention is deemed to be beneficial.

12.13 Publication Policy

12.13.1 Trial Results

The results of the trial will be disseminated regardless of the direction of effect.

12.13.2 Authorship

Ownership of the data arising from the study resides with the trial team. The publication policy will be in line with rules of the International Committee of Medical Journal Editors. The TMG will decide on authorship with any difficulties being resolved by the TSC.

13 Ancillary Studies

None at present.

14 Protocol Amendments

This is version 1.1 of the protocol: Only minor administrative changes have been made throughout the protocol version 1.0.

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