IMP²ART

IMPlementing IMProved Asthma self-management as Routine

Statistical Analysis Plan (SAP)

Version: 1.0

Date: 13 December 2025

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1. Administrative Information

1.1 Person(s) contributing to the analysis plan

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Position	**Chief investigator**
Name	Professor Hilary Pinnock
Signature	
Date	12/12/2025
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Date	
Position	**Independent statistician**
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Tick once reviewed	✓
Date	05/12/2025

1.2 Trial information

The IMP²ART study (P243) registration number is ISRCTN15448074. This SAP was written in conjunction with protocol version 4.0 (dated 19/APR/2022). This SAP will be amended if it is impacted by any subsequent amendments to the protocol.

1.3 SAP revision history

Protocol version*	Updated SAP version no.	Section number changed	List/description of changes from previous version/protocol	Justification for revision†	Author of change	Date
4.0	1.0	ALL	-	-		13/12/25

1.4 Members of the writing committee

The statistical analysis plan writing committee comprises, Beth Stuart (BS) and Thomas Hamborg (TH). Kamran Khan and Rianna Mortimer contributed to an earlier draft. Input was provided by Hilary Pinnock and Steph Taylor. BS and TH are primarily responsible for writing and implementing the statistical analysis strategy.

1.5 Timing of SAP revisions in relation to unblinding of data/results

Versions of the SAP up until version 1.0 were written whilst contributors did not have access to unblinded trial data or trial results by treatment group. The trial statistician will perform the analysis without knowledge of allocation group names (groups will be coded as X and Y for the analysis until satisfactory coding has been implemented). Any potential deviations from the agreed SAP can be discussed with the fully blinded senior, or independent statistician, to ensure decisions are not influenced by the data or emerging results.

1.6 Timing of statistical analysis

The statistical analysis is conducted once the SAP has been signed off, the last participating practice has completed the last follow-up, the data have been cleaned and the randomisation database locked.

1.7 Remit of SAP

This document aims to detail statistical analyses and presentation of results of the clinical and implementation effectiveness analysis of the IMP²ART trial. This SAP does not include health economic analyses, or the process evaluation associated with the IMP²ART trial. These analyses will be/are described in separate documents[1].

1.8 Public availability of the SAP

The SAP will be made available on Open Science Framework (OSF) and the trial registration page.

1.9 Statistical software

Analyses and data presentation described in this document will be performed using R version 4.5.1 or later and Stata v18.0, unless otherwise specified.

1.10 Abbreviations

Abbreviation	Meaning
ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
A&E	Accident and Emergency
AUKCAR	Asthma UK Centre for Applied Research
BCC	Barts Cancer Centre
BMJ	British Medical Journal (BMJ Learning is a professional educational resource)
CHI	Community Health Index
CI	Confidence Interval
COM-B	Capability, Opportunity, Motivation → Behaviour
CRF	Case report form
DIRUM	Database of Instruments for Resource Use Measurement
EfH	Education for Health
EHR	Electronic Health Record
EQ-5D-5L	EuroQol – 5 Dimensions – 5 Level (and corresponding version for youths: EQ-5D-Y)

Abbreviation	Meaning
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations
GEE	Generalised Estimating Equation
GP	General Practitioner
HS&DR	Health Service and Delivery Research
ICH	International Conference on Harmonisation
IMP2ART	IMPlementing IMProved Asthma self-management as Routine
ICC	Intra class correlation
IEE	Independent Estimating Equations
i-PARIHS	Integrated-Promoting Action on Research Implementation in Health Services
IT	Information Technology
LTC	Long Term Conditions
MRC	Medical Research Council
NHS	National Health Service
NIHR	National Institute of Health Research
OPC	Optimum Patient Care
OPC ID	The ID code applied by OPC to anonymise extracted data
OPCRD	Optimum Patient Care Research Database
PCTU	Pragmatic Clinical Trials Unit

Abbreviation	Meaning
PDG	Programme Development Grant (Phases: PDG1, PDG2, PDG3)
PG	Programme Grant (Phases: PG1, PG2/3, PG4, PG5, PG6)
PPI	Patient and Public Involvement
PCRS	Primary Care Respiratory Society
QA	Quality Assurance
QALY	Quality-adjusted life year
QMUL	Queen Mary University of London
R&D	Research and Development
RCP3Qs	Royal College of Physicians 3 Questions
REC	Research Ethics Committee
RCT	Randomised Controlled Trial
SFTP	Secure File Transfer Protocol
SMF	Study Master File
SOP	Standard Operating Procedures
StaRI	Standards for Reporting Implementation Studies
UK	United Kingdom

1.11 Summary of the Trial

Trial Information	
Chief Investigator	Professor Hilary Pinnock
Sponsor Name	The University of Edinburgh and Lothian Health Board, ACCORD Royal Infirmary of Edinburgh 47 Little France Cres, Edinburgh EH16 4TJ,
Sponsor Number	AC19081
REC Number	19/EM/027904/02/2020 and *ADEPT1619*
Trial Design	
Study Design	Cluster randomised parallel group, hybrid II implementation trial
Study Objectives	To test in a national cluster RCT the impact of a whole systems implementation strategy to embed supported asthma self-management in routine primary care compared with usual care, on: a) Proportion of people with active asthma who have an unscheduled asthma consultation recorded in their electronic health record (EHR) in the second year post-randomisation (the primary clinical outcome). b) Proportion of people with active asthma who have a record in their EHR of the provision/updating of an action plan in the prior 2 years assessed at 24m post-randomisation (the implementation outcome). c) Secondary outcomes (ownership of an action plan reported in the Quality Improvement questionnaire (QI-Q), number of asthma reviews conducted, prescribing of reliever medication and oral steroids, asthma symptom control, patients' confidence in self-

	management and professional support, unscheduled care in the 1st year post randomisation, GINA control).
Setting	GP practices in England and Scotland and their Asthma patient population
Target Sample Size	144 GP practices (the unit of randomisation) comprising ~ 14,000 participants per arm = 28,000 in total are required for the primary clinical outcome as per sample size calculation.
Population	General practices in the UK (England and Scotland) using one of four common EHR systems. The eligible patient population includes all individuals with a diagnosis of 'asthma' who have been on the 'active asthma' register of the practice throughout the 3-year data collection period (1-year pre-trial and 2-years during the trial), excluding those under 6 years of age at the point of randomisation, those under the care of a severe/difficult asthma clinic, those with significant co-morbid chronic obstructive pulmonary disease (COPD), and those on the palliative care register or identified by the practice as clinically unsuitable. Aligned with the Quality and Outcome Framework, 'active asthma' is defined as a coded diagnosis of asthma at any point in the past and having been prescribed an asthma medication in the prior 12 months.
Intervention	Implementation of the IMP²ART strategy, which includes organisational resources, training for professionals, and resources to support patients in self-managing their asthma. This strategy is facilitated by nurse specialists and involves a workshop and up to 12 hours of contact time over 12 months.

Comparator	Usual care provided by general practices without the additional IMP²ART implementation strategy.
Treatment duration per participant	The treatment duration is 2 years. The implementation strategy is directed at the practice level; the participants are thus the practices not individual patients. The implementation strategy is delivered during the first year with practices expected to receive the facilitation workshop in the first six months after randomisation. Duration is considered to be 2 years as the intervention is intended to lead to changes in systems and processes which will still be present after the year 1 implementation phase.
Outcomes	***Primary clinical outcome from EHR:*** The primary clinical outcome is having at least one episode of unscheduled care for asthma (GP consultation; and/or out-of-hours attendance; A&E attendance; hospital admission) within the second-year post-randomisation (yes/no). ***Primary implementation outcome:*** Having a record in the EHR of the provision/updating of an action plan in the prior 2 years assessed at 24m post-randomisation (yes/no) ***Secondary outcomes:*** Unless otherwise stated these will be assessed at both 12m and 24m **Ownership of an Asthma Action Plan from QI-Q** • Self-reported provision of an action plan in the QI-Q in the period 9 months to 21 months post-randomisation (yes/no) **Asthma Symptom Control from EHR** • Having good asthma control (yes/no) as measured by the Royal College of Physicians 3 Questions

	(RCP3Qs), Asthma Control Test (ACT), Children's ACT (C-ACT) or Asthma Control Questionnaire (ACQ). • Count of reliever inhalers prescribed in the previous year. **Asthma Attacks from EHR** • Incidence of asthma attacks defined as the proportion experiencing unscheduled care in the first year after randomisation). • Proportion of individuals prescribed a course of oral steroids in the past 12 months. • Number of steroid courses per patient per year. • Number of asthma exacerbations in past year **'GINA Control' Assessment from EHR** • Binary composite outcome of well controlled asthma consisting of GINA control analysed as a binary variable which is set to 1 if three components are all 'yes' and set to 0 otherwise. Components: - no night-time symptoms or activity limitation (from the coded RCP3Qs), - symptoms/requirement for rescue medication less than two doses per week (from prescribing record) - no attacks in the previous year (unscheduled care from EHR). **Asthma Management from EHR** • Having received an annual asthma review in the prior 12 months (yes/no). **Prescribing Outcomes from EHR**

	• Proportion of individuals prescribed inhaled steroids (either as an ICS inhaler, or as a combination ICS/LABA) and the number of prescriptions per year. • Proportion of individuals prescribed reliever medication (defined as SABA inhalers and the number of prescriptions per patient per year. • Proportion of individuals using a sub-optimal treatment regimen, defined as a ratio of controller medication prescriptions to total asthma medication prescriptions less than 0.5. **Confidence in self-management and professional support from QI-Q** • Asthma Bother Profile (management section) to reflect the quality of asthma care and patient confidence in self-management on a scale from 0 (no confidence) to 5.

2. Introduction

2.1 Background and rationale

An estimated 3.6 million people in the UK are actively being treated for asthma[4] . Each year, asthma is responsible for over 6 million primary care consultations, nearly 100,000 hospital admissions[4] over 1,000 deaths (20 a year in children under 14 years),[5] at a cost to the NHS in England and Wales of at least £1billion [4]. Societal costs accumulate throughout life with asthma-related absence from school or work, disability and premature retirement. Much of this morbidity is preventable with appropriate/timely (self)management. [6–8]

Our systematic meta-review, funded by the National Institute for Health and Care Research (NIHR) Health Service and Delivery Research (HS&DR), synthesised evidence from 27 systematic reviews (270 RCTs) and concluded that supported self-management reduces hospitalisations, accident and emergency (A&E) attendances and unscheduled consultations, and improves markers of control and quality-of-life for people with asthma[9].

A personalised asthma action plan, developed during a self-management discussion and regularly reviewed, empowers patients to identify worsening symptoms and take appropriate measures, such as adjusting medication or seeking medical assistance[10–12]. The cost of providing self-management support, estimated as a two-hour investment in the first year according to a recent network meta-analysis[13], is balanced by the reduction in hospital admissions and unplanned healthcare visits[9]. Supported self-management has proven effective across various cultural groups[14–17], including children (excluding pre-school children)[18–20], adolescents[21,22], adults[10], and the elderly[23,24], and in both primary and secondary healthcare settings[25–28].

For three decades[29], national and international guidelines have consistently recommended that individuals with asthma receive self-management education, reinforced by a personalised action plan and supported by regular reviews with healthcare professionals[6,8,30]. However, implementation in routine clinical practice remains inadequate. Surveys from the UK, USA, Northern Europe, and Australia indicate that less than one-third of asthma patients have an action plan[31–33]. Our developmental work using routine primary care data showed that only 6% had documentation of being provided with an action plan in the EHR[34]. The 2014 UK National Review of Asthma Deaths highlighted that half of those who died had not sought medical help, underscoring the critical importance of asthma self-management for timely response to worsening asthma control[35].

Addressing this issue requires a comprehensive system-wide approach[36]. A systematic review funded by NIHR HS&DR on implementing supported self-management concluded that while patient education,

professional training, and organisational support are all crucial, they are rarely effective when used alone[37]. Effective implementation involves multiple facets and disciplines, engaging patients and motivating professionals within an organization that actively supports self-management[38]. A systematic review of asthma implementation studies[38] identified small randomized controlled trials focusing on either patient education, professional training, or organizational support and observational studies reporting on system-wide initiatives, including some large-scale national projects[39,40]. However, there are no randomised trials evaluating whole-system implementation strategies—a gap that the current study seeks to fill.

2.2 Aims & Objectives

Primary Aim: To determine whether the facilitated delivery of the IMP²ART strategy increases the provision of asthma action plans and reduces unscheduled care in routine UK primary care settings.

Objectives:

1. **Primary Clinical Objective:**
    - To assess and draw inference on the between-group difference in unscheduled asthma care in the second year after randomisation (between 12- and 24-months post-randomisation) using EHR data.
2. **Primary Implementation Objective:**
    - To assess and draw inference on the between-group difference in the EHR recorded provision/updating of an action plan in the 2-year period from baseline to 24 months post-randomisation.
3. **Secondary Objectives:**

    To assess and draw inference on the between-group differences in secondary outcomes listed in 3.5.

3. Study methods

3.1 Trial design

This is a UK-wide parallel group, cluster randomised controlled hybrid II implementation trial addressing both clinical and implementation outcomes. The randomisation is at the general primary care practice level and involves the random assignment of 144 general practices across England and Scotland to either the IMP²ART implementation strategy or the usual care control group. The implementation strategy includes a facilitation workshop, organisational resources, training for healthcare professionals, and patient support tools aimed at enhancing asthma self-management.

3.2 Planned interim analyses

No interim analyses will take place during the trial as the routine data will not be extracted until the end of the trial, and there is no data monitoring and ethics committee. Randomisation and timing of implementation of trial-related procedures is monitored.

3.3 Randomisation procedure

Randomisation will be at the level of general practice using remote online randomisation facilitated by the Pragmatic Clinical Trials Unit (PCTU) at Queen Mary University of London. A 1:1 allocation ratio is employed to assign practices to either the implementation or control group within randomly permuted blocks of sizes 4 and 6. Binary stratification factors are deprivation status, practice size, and GP training status to ensure a balanced allocation. After randomisation to trial arm, practices are randomised to conducting or not conducting quality improvement data collection with a 13:5 (no: yes) ratio, thereby selecting a total of 32 practices for the QI-Q data collection, ensuring an even distribution between the two groups. The randomisation process is implemented using REDCap software, with allocations requested by the programme manager.

3.4 Sample size calculation

Primary Clinical Outcome: Unscheduled Care

The sample size calculation for the primary outcome of unscheduled care is based on a baseline rate of 34% for unscheduled care among asthma patients. The study aims to detect a clinically significant absolute difference of 7%, reducing the rate from 34% to 27% between the intervention and control groups. To achieve this a total of 1,868 patients would be required in each group (without accounting for clustering) to maintain a power of 90% and a significance level of 5%.

Considering an intraclass correlation coefficient (ICC) of 0.07, derived from previous pragmatic implementation studies, and assuming an average cluster size of approximately 200 patients per practice, the trial will require 70 practices per arm (a total of 140 practices). To account for potential practice withdrawals, this number is increased to 72 practices peer arm, resulting in a total recruitment target of approximately 14,000 patients across both arms.

Originally the intention was to recruit only practices with a list size of >6000 (assuming 6% will have active asthma) to avoid cluster sizes of <200. However, during the recruitment, it became clear that this will exclude many small rural general practices in Scotland, and therefore, we decided to allow variable cluster sizes (including a few clusters likely to be <200). Also, the COVID-19 pandemic resulted in a reduction in asthma attacks[41,42] and an analysis of the OPC dataset (n=286 practices) in September 2021 showed that 25.8% was a more realistic estimate of the proportion with unscheduled care that we could expect in the control group. Maintaining the recruitment target of 144 practices (140 after loss to follow up) and allowing for a variable cluster size (mean = 200; coefficient of cluster size variation = 0 .8), the study would have 94.7% power to detect a reduction from 25.8 to 18.8%.

Implementation Outcome: Asthma Plan Ownership/Provisions

The definition of the primary implementation outcome has changed. The a-priori sample size calculation is thus not applicable but is retained here for completeness. The justification for this change is provided in section 3.5. As the new primary implementation outcome is obtained from the EHR a sample size substantially larger than the required sample size calculated below is expected.

For the implementation outcome regarding asthma action plan ownership, data from previous studies indicated a baseline prevalence of 34%. The study anticipates a 15% increase in ownership due to the IMP²ART intervention, leading to an expected ownership rate of 49%. The effect size calculated for this increase is h = 0.322.

To achieve a power of 90% with a significance level of 5%, the sample size required without clustering is estimated at 203 patients per arm, resulting in a total of 406 patients for the randomised controlled trial. However, accounting for an ICC of 0.03 and requiring at least 20 completed questionnaires from each cluster, the total number of clusters needed is set at 32 (16 practices per arm). Thus, the overall target sample size for this outcome is approximately 640 patients.

Given an expected response rate of around 45%, questionnaires will be dispatched to about 50 participants per practice to ensure adequate data collection.

3.5 Outcome definitions

CHANGE OF DEFINITION OF THE PRIMARY IMPLEMENTATION OUTCOME

Our primary implementation outcome (asthma action plans) is a marker of supported self-management, and our protocol defined two complementary approaches for assessing this.

- *Ownership of an action plan reported in a random sample of patients from a random sample of practices at 12 months post-randomisation*. This was originally defined as the primary implementation outcome because it avoided any potential influence of IMP²ART on clinical coding practice. However, challenges with arranging timely mailing of the QI-Q combined with a 23% response rate meant that we achieved only 223 responses (35% of our target sample size of 640) In addition, the responders were older and more likely to be female than the whole population.
- *Proportion of people with asthma who have a record in their EHR of the provision/updating of an action plan in the previous 3-years assessed at 12-months post-randomisation*. This has the advantage that it uses data from all eligible patients from all participating practices (the preferred option in implementation research). However, because of concerns that use of the IMP²ART template might bias recording in the implementation group it was originally defined as a secondary implementation outcome.

In the event, our process evaluation shows few practices actually used the template (because many NHS Trusts incentivised use of alternative clinical templates). We therefore switched our primary implementation outcome to 'Proportion of people with active asthma who have a record in their EHR of the provision/updating of an action plan in the previous 2 years assessed at 24m post-randomisation' and relegated the alternative approach 'Ownership of an action plan reported in the QI-Q' to a secondary outcome.

The change to a two-year time window ensures that the full intervention effect is captured regardless of the rate at which the practice adopted the implementation strategy, replacing the three-year time window that was suggested by the IMP²ART patient colleagues as 'reasonable' rather than based on evidence. In addition, removing the 3rd year from the outcome reduces the influence of the COVID period which substantially affected provision of asthma care.

Primary Objective	Primary Endpoint	Outcome measure
To determine whether the facilitated delivery of the IMP²ART strategy reduces unscheduled care in routine UK primary care settings	Participant level: A binary outcome of having at least one unscheduled care visit (e.g., emergency department visits, hospital admissions) vs. having no unscheduled care visit within the second-year post-randomisation.	The marginal, participant-average between-group difference in unscheduled care in the second year after randomisation (12 to 24 months post-randomisation) assessed from routine data. Analysis approach: Absolute risk difference estimated using GEE with a working independent correlation structure alongside an identity link function and Gaussian family cluster-robust (VCE) standard errors will be used.
To determine whether the facilitated delivery of the IMP²ART strategy increases asthma action plan provision	A binary (Y/N) endpoint of EHR provision/updating in the previous 2 years assessed 24 months post-randomisation.	Marginal cluster-average between-group difference in asthma action plan provision percentage at in the previous two years assessed at 24 months post-randomisation. Analysis approach: GEE-Gaussian with identity link function for risk difference with independence correlation and robust SE. Inverse cluster-size weights equal to 1/(cluster size) will be used to give equal weight to each cluster.

Secondary Outcomes

Secondary Objective	Secondary Endpoint	Outcome measure
To determine whether the facilitated delivery of the IMP²ART strategy increases the ownership of asthma action plan	Ownership of an action plan is defined as the proportion of people with asthma (≥ 5 years of age) who respond 'Yes' to the question 'Has your asthma nurse or doctor provided you with an asthma "action plan"?' in the QI-Q mailed at 12 months.	Marginal cluster-average between-group in asthma action plan ownership percentage at 12 months post-randomisation. Analysis approach: GEE-Gaussian with identity link function for risk difference with independence correlation and robust SE. Inverse cluster-size weights equal to $1/nj$ will be used to give equal weight to each cluster.
To analyse the prescribing outcomes, including reliever medication and oral steroids.	Number of prescriptions (count) for preventer and/or reliever medication Number of prescriptions (count) for oral steroids per patient in routine data. • Proportion of individuals prescribed inhaled steroids (either as an ICS inhaler, or as a combination ICS/LABA) • Proportion of individuals prescribed reliever medication • Proportion of individuals using a sub-optimal treatment regimen, defined as a ratio of controller	Participant-average between group difference, analysed at 12- and 24-months post-randomisation using IEE with Negative Binomial distribution and log link.

	medication prescriptions to total asthma medication prescriptions less than 0.5.	
To assess asthma symptom control	Asthma symptom control measured by a validated questionnaire, (RCP3Qs from routinely collected EHR data where three "no" responses means that asthma symptoms are well controlled[45] or ACT/C-ACT where a score ≥ 20 is 'well controlled'[46]. • GINA control (binary) which is set to 1 if three components are all 'yes' and set to 0 otherwise.	Analysed using IEE with ordinal logistic regression.
To evaluate patients' confidence in self-management	Confidence level assessed via a self-reported scale (0-5).	Average confidence score reported by patients at follow-up compared to baseline, analysed at both 12- and 24-months post-randomisation using IEE with ordinal logistic regression.

All outcomes collected via routine data are based on READ or SNOMED codes (see Appendix 8.1)

3.6 Timing of outcome assessments

The primary clinical outcome of unscheduled care will be assessed at the patient level using routine data collected over a three-year period: one year pre-trial and two years during the trial. This outcome consists of all unscheduled care events (or absence of an event) over a time-period rather than an assessment at a

fixed time point. The primary clinical outcome analysis time-period is the second year after practice randomisation (12 to 24 months post-randomisation).

For the primary implementation outcome of asthma action plan ownership recorded in EHR, data will be collected using routine data collected over the three year period and assessed for a record of the provision or updating of an action plan (yes/no) in the previous 2 years, assessed at 24 months post-randomisation.

Secondary outcomes, including the number of asthma reviews conducted, prescribing outcomes, asthma symptom control, and patients' confidence in self-management, will be assessed at both 12- and 24-months post-randomisation. The baseline, first year and second year after randomisation will be defined using the date of randomisation for each cluster. For routine data collection, all data within the specified time periods will be included in the analysis.

For the secondary outcome of self-reported possession of an action plan using the QI-Q data, questionnaires are sent out by an in-house OPC system. This process could only be initiated after randomisation (because allocation to the QI questionnaire was only determined after randomisation). The process is complex and required active engagement of administrative/IT and clinical staff in the practices resulting in a considerable delay for some practices. Blinded assessment of questionnaire response rates revealed lower than anticipated return rates and delay of returns by patient. The following pragmatic time window is therefore chosen for questionnaire outcomes (at the 12- and 24-months time points):

- Lower cut-off: time point – 3 months regardless of whether questionnaires we initially classified as baseline, 12m or 24,
- Upper cut-off: time point + 9 months regardless of whether questionnaires were initially classified as 12 or 24m

This is an average of 3 months after the baseline/12m/24m time-point, which aligns with the average time to taken to set up the facilitation workshop in practices allocated to the implementation group

4. Statistical Principles

4.1 General analysis principles

The analysis of the primary and secondary outcomes will follow principles set out in the estimand framework. Each main analysis of primary or secondary outcomes will adjust for all cluster-level randomisation stratification factors (deprivation status (above vs below or equal to median IMD), practice size (small vs large (>8035 list size)), GP training status (training practices yes/no)) using direct adjustment. If convergence issues arise due to the number of covariates, we will implement a hierarchical approach to removing variables from the model:

First, we will attempt to fit the full model with all stratification factors.

If convergence problems occur, we will prioritise retaining factors based on their expected impact on outcomes:

a. Deprivation status

b. Practice size

c. GP training status

Factors will be dropped in reverse order of priority (c, then b, then a) until the model converges.

If dropping all stratification factors still results in convergence issues, alternative modelling approaches described in section 6.3 will be used.

For the analyses of the primary and secondary outcomes, the following information will be presented.

- The number of practices and patients included in each analysis, by treatment arm
- A summary statistic of the outcome (e.g. frequency (%) or mean (SD) by treatment arm
- The estimated treatment effect as a risk difference (main) and odds or rate ratio; or mean difference for count variables
- A 95% confidence interval for the estimated treatment effects
- A two-sided p-value
- The estimated ICC

The significance level for statistical tests will be 5%, i.e. no adjustment for multiple comparisons will be made. The number of comparisons will be taken into account in the interpretation of results, in particular when hypothesis tests for primary outcomes are non-significant but secondary outcomes are.

The analysis will follow the intention-to-treat principle, with practices analysed according to their randomised group assignment, regardless of the level of implementation of the IMP²ART strategy, unless otherwise stated. No (multiple) imputation will be performed for missing data (see section 6.4). Data for the majority of EHR-derived outcomes (including the primary outcomes) cannot be missing at the patient-level as they are defined as the presence or absence of an event code.

Any deviations from the planned analysis set out in the SAP will be documented in the statistical report under the section *Deviations from the Statistical Analysis Plan.*

4.2 Fidelity and adaptation of the implementation strategies

In an implementation trial, variable adoption is expected, and adaptation of the implementation strategies to enable embedding of the supported self-management intervention in the routine of individual practices is encouraged. The process evaluation will be monitoring and describing this in detail. Core components of the implementation strategy to which fidelity is expected are:

1. A facilitator workshop, delivered on-line to the practice team
2. Monthly audit and feedback reports monitoring progress delivering action plans
3. Completion of the team education module
4. Completed of the on-line education module by clinicians
5. Access to the Living with Asthma website

Receipt and use of these implementation components will be presented in a summary table by treatment group; adaptation will be captured qualitatively in the process evaluation (not part of the statistical analysis report). The impact of adoption of these core components on the treatment effect is assessed in a CACE analysis described in section 6.7.

4.3 Protocol deviations

The intervention is targeted at GP practices, and all recorded deviations occur at practice level. Protocol deviations are defined as any instances where trial procedures are not adhered to. The following categories will be tabulated:

- Instances where a practice is inadvertently assigned to an incorrect treatment group or randomised in error.
- Any variations from the stratification factors used during randomisation.
- Failed collection of routine data or failed mailing of QI-Qs

Protocol deviations not falling in one of the above categories will be classified as 'other' and individually described.

4.4 Methods and assumptions for dealing with data anomalies

- Outliers: Extreme values could potentially arise in the form of an implausibly high number of events in a patient's EHR (e.g. a very high number of appointments or prescriptions). All events identified through pre-specified code lists will be included in the main analysis. Sensitivity analyses excluding confirmed outliers counts will be conducted if necessary. Potential outliers will be identified by the statistics team. They will be presented to the CI and clinical members of the

TMG without revealing participant's group allocation, who will then decide if the value constitutes an outlier. Both primary outcomes are binary variables (and events vs none) and therefore won't be affected.

- Inconsistent data: Any logically inconsistent data (e.g., contradictory responses) will be recorded in an appendix to the statistical analysis report together with rules for handling such inconsistencies.

5. Trial population

The trial population consists of two levels, GP practices and patients within practices.

5.1 Practice eligibility

5.1.1 Inclusions criteria

- General practices in England or Scotland
- Using one of four common EHR systems: EMIS, SystmOne, Vision, or Microtest
- Agreeing to Optimum Patient Care (OPC) extracting anonymised routine coded data
- Practices with successful data extraction demonstrating no insurmountable governance or technical problems

5.1.2 Exclusions criteria

- Very small practices likely to have substantially fewer than 200 patients with 'active asthma' registered throughout the trial
- Practices undertaking research or initiatives that might affect the study outcomes
- Practices that work closely with another participating practice (e.g., as part of a network or federation)

5.2 Patient eligibility

5.2.1 Inclusions criteria

- Aged 6 years or over (on the date when the practice was randomised)
- Have a coded diagnosis of 'asthma' and have been on the 'active asthma' register of the participating practice throughout the 3-year data collection period for the

trial. 'Active asthma' is defined by the Quality and Outcome Framework as having a coded diagnosis of asthma and having been prescribed an asthma medication within the previous year[2].

5.2.2 Exclusions criteria

- Under 6 years of age on the date when the practice was randomised
- Under the care of a severe/difficult asthma clinic
- Having significant co-morbid chronic obstructive pulmonary disease (COPD) defined as a code of COPD and prescribed a LAMA (including combination inhalers)
- Patients whose electronic health record is coded as not wanting their data used for any other purpose than their care
- Being on the palliative care register

5.3 Analysis population

The primary analysis set will be the intention to treat population. Practices are analysed according to their randomised group assignment, regardless of the level of implementation of the IMP²ART strategy or alternative asthma management in the control group during the trial. Individual patients are part of the analysis set if they have a diagnosis of 'asthma', are on the 'active asthma' register of the practice throughout the 3-year data collection period (1-year pre-trial and 2-years during the trial) and fulfil other inclusions and exclusions criteria. The patient cohort is derived from a transfer of all patients with a coded diagnosis of asthma in participating practices facilitated by OPC. This derivation is a 10-step process described in Appendix 8.1.

5.4 Participant flow

Participant flow through the trial will be summarised by an adapted CONSORT flow diagram for cluster randomised trials. This will include the numbers: screened, consented and randomised clusters. It will further include clusters withdrawn or lost to follow-up, and individual participants included in the analysis of the primary outcomes . See Appendix for a draft CONSORT diagram.

5.5 Withdrawals

Participating practices are free to withdraw from the IMP²ART study at any point without providing a reason. Withdrawal from the intervention or follow-up will be clearly defined as follows:

- **Active Withdrawal:** This occurs when a practice formally communicates their decision to discontinue participation in the study. The timing of active withdrawals of practices will be recorded, including the date of withdrawal and any reasons provided, where available.
- **Loss to Follow-Up:** There are potential reasons why data extraction may be unsuccessful, despite only randomising practices after a successful data extraction, there may be insurmountable technical problems. A practice merger could mean that data from the original participating practice cannot be extracted.

The number (percentage), timing (mean and standard deviation of weeks since randomisation), and reasons for withdrawal will be summarised by treatment group.

5.6 Baseline characteristics

Demographic and clinical characteristics at baseline will be summarised by treatment group (IMP²ART implementation strategy vs. usual care). Practice-level demographic information will include:

- Practice list size
- Deprivation status
- GP training status
- Number of patients with 'active' asthma

These will be presented as mean (SD) for continuous variables and n (%) for categorical variables. Patient-level demographic information will include:

- Age
- Sex
- Comorbidities hypertension, diabetes, cardiovascular disease, COPD

Age will be presented as mean (SD), while sex and comorbidities will be presented as n (%). Clinical outcomes at baseline will include (in the year prior to randomisation):

- Proportion of patients with unscheduled care event
- Proportion of patients with EHR record of an asthma action plan
- Number of asthma reviews conducted (percentage or number per patient)
- Prescribing of preventer and/or reliever medication and oral steroid courses

- Asthma symptom control (as measured by the symptom control composite and GINA control))
- Patients' confidence in self-management (from the QI-Q).

Normally distributed data will be summarized by mean (SD), while non-normally distributed data will be presented as median (IQR). The proportion of patients with an asthma action plan will be presented as n (%). Health economics and healthcare use data will be summarised separately in a Health Economics Analysis Plan (HEAP) created by the Health Economics team.

5.7 Other data summaries

Additional descriptive data summaries will include:

1. Concurrent medications: A summary of any changes in asthma medication prescriptions during the follow-up period will be provided. This will include:
    - Changes in reliever medication prescriptions
    - Changes in preventer medication prescriptions
    - Prescriptions of oral steroids
2. Asthma review completion: A summary of the proportion of patients with an annual asthma review conducted in each group during the trial period.
3. Practice characteristics: A summary of practice-level characteristics that may influence implementation, such as:
    - Practice size
    - Urban/rural location
    - Deprivation status of the practice area
    - Previous participation in asthma-related quality improvement initiatives

6. Analysis

6.1 Interim analysis

No interim analyses are planned.

6.2 Estimand framework

The primary estimand for the IMP²ART trial can be defined as in the following table.

Objective The primary objective of the IMP²ART trial is to evaluate the effectiveness of the IMP²ART implementation strategy in increasing the provision of asthma action plans and reducing unscheduled care (delivered in any setting) recorded in routine UK primary care settings. Specifically, the trial aims to compare the outcomes of practices implementing the IMP²ART strategy against those continuing with usual asthma care.	**Definition** The difference in rates of unscheduled care visits (e.g., unscheduled GP consultations, emergency department visits, hospital admissions) between practices receiving the IMP²ART implementation strategy and those receiving usual care, assessed between 12- and 24-months post-randomisation. Additionally, the primary implementation outcome will measure the record in the EHR of the provision/updating of an action plan .
Estimand	
Target population The target population consists of general practices in England and Scotland that are eligible for participation in the trial and all patients with 'active' asthma (6 yrs and over at the point when the practice is randomised) within these practices.	**Practices:** General practices in England and Scotland that are eligible for participation in the trial. **Patients:** Patients aged ≥6 years from participating practices o With a code of asthma in their medical records o Who have received a prescription for asthma medication in the previous year.

Variable/endpoint The primary endpoint is the rate of unscheduled care visits assessed from routine data during the second-year post-randomisation (12 to 24 months). The primary implementation outcome is the proportion of people(≥5yrs) with a record of having been given an asthma action (or updated) plan at 24 months, post randomisation.	The between-group difference in unscheduled care in the second year after randomisation (12 to 24 months post-randomisation) assessed from routine data. Proportion of people with active asthma who have a record in their EHR of the provision/updating of an action plan in the previous 2 years assessed at 24m post-randomisation
Treatment conditions	**Intervention group-** The treatment being evaluated is the IMP²ART implementation strategy, which includes organisational resources, training for healthcare professionals, and patient support tools aimed at enhancing asthma self-management. **Control arm-** The comparator treatment is usual care provided by general practices without the additional IMP²ART intervention
Population level summary measure	Primary clinical outcome: Marginal participant-average treatment effect - difference in proportion of unscheduled care between intervention and control groups, presented with 95% confidence intervals and two-sided p-values Primary implementation outcome: Marginal cluster-average effect - difference in proportion of patients with an asthma action plan between intervention and control groups
Intercurrent events	**Strategy**
Practice withdrawals: Practices may withdraw from the study at any point.	**Treatment policy** strategy, where practices will be analysed according to their original randomised group regardless of withdrawal.

Change in asthma medication or management outside of trial	**Treatment policy strategy**, analysing patients based on their practice's assigned group regardless of medication use
Poor adoption of the IMP²ART strategy: Some practices in the intervention group may not engage with the IMP²ART strategy.	**Treatment policy strategy**, analysing practices based on their assigned group regardless of adherence level.
Changes in asthma medication or management: Patients may experience changes in their asthma treatment outside of the trial intervention	**Treatment policy strategy**, including all patients in the analysis regardless of treatment changes.
Social distancing measures making it less likely that a participant can or will seek unscheduled care	**Treatment policy strategy**
Social distancing measure changing participant behaviour leading to lower than 'normal' unscheduled care rates.	**Treatment policy strategy**
Incorrect coding of unscheduled care in EHR system	**Treatment policy strategy**

6.3 Analysis of primary and secondary outcomes

Primary Clinical Outcome: Unscheduled Care

- Method of analysis:

  1. Unweighted Independence estimating equations (IEE) with cluster-robust standard errors (at practice level) and GEE-Gaussian with identity link function. This methods has been found to be unbiased and minimises the empirical standard error.[44] An independent working correlation structure and a constant variance structure will be used.

  2. Unweighted Independence estimating equations (IEE) with cluster-robust standard errors (at practice level) and using GEE with a Binomial distribution and logit link function. An independent working correlation structure and a constant variance structure will be used.
- Treatment effect presentation: Absolute risk difference (method 1) and odds ratio (method 2) with 95% confidence intervals and p-value.
- Baseline covariates at cluster-level: Practice list size, deprivation status, GP training status.

Primary Implementation Outcome: Asthma Action Plan provision

- Method of analysis: Methods 1 and 2 described for the primary clinical outcome but with weighting at individual-level by (1/cluster size) to obtain cluster-average estimates.

- Treatment effect presentation: Absolute risk difference (method 1) and odds ratio (method 2) with 95% confidence intervals and p-value.
- Baseline covariates: Practice list size, deprivation status, GP training status.

Secondary Outcomes:

Unless otherwise stated, the secondary outcomes will be analysed using routine data at baseline, 12 months and 24 months

Asthma symptom control

Proportion well controlled on asthma symptom questionnaires and mean number of reliever inhalers prescribed between intervention and control group patients. The analysis will be at the patient-level using unweighted IEE.

Asthma Attacks

Number of asthma attacks defined as the number of unscheduled care events in the previous year i.e. first year after randomisation. The analysis will be performed using IEE with Negative Binomial distribution and log link function for the number of asthma attacks as incidence rate ratio and marginal mean difference between intervention and control group at patient-level. Number of asthma exacerbations in past year (READ code XaINh and equivalent SNOMED code 366874008) will be analysed using the same models. Proportion of individuals prescribed a course of oral steroids in the past 12 months will be analysed using the primary clinical outcome methods 1 & 2.

GINA control

The outcome of 'GINA control', will be assessed as a composite outcome. The GINA guidelines define control over a period of 4 weeks as no night-time symptoms or activity limitation, symptoms/requirement for rescue medication < 2 doses/week, and no attacks in the previous year. We will analyse the proportion of people achieving GINA control using IEE implementation in GEE model with binomial distribution and logit link function odds ratio between intervention and control groups and the analysis will be at the patient-level.

The odds ratio represents the odds of achieving GINA control in the intervention group compared to the control group. An odds ratio greater than 1 would indicate higher odds of GINA control in the intervention group, while an odds ratio less than 1 would suggest lower odds compared to the control group.

Asthma management

Proportion of people with active asthma reviewed annually and proportion of people with record of provision of an action plan, assessed at 12 months and 24 months post-randomisation using IEE.
Annual review proportion: IEE using GEE with binomial distribution and logit link function.
Action plan provision: IEE using GEE with binomial distribution and logit link and reported as odds ratios between intervention and control group practices. We will target cluster-level outcome using weighted IEE on participant-level data (weight = 1/cluster size) or unweighted cluster-level analysis.

Prescribing Outcomes

Proportion of people prescribed inhaled steroids, reliever medication and number of prescriptions per year. The number of prescriptions will be analysed using an IEE model with Negative Binomial distribution and log link function, presented as marginal mean difference and rate ratio between intervention and control practice groups. Binary prescription outcomes will use the primary clinical outcome analysis model.

Confidence in self-management and professional support (from the QI-Q)

The asthma bother profile (management section) reflects quality of asthma care and patient's confidence in ability to self-manage on a scale of 0 (no confidence) to 5. This outcome will be analysed by utilising IEE using GEE model with ordinal logistic regression.
The outcome of professional support will be analysed using IEE implementation in the GEE model at the practice (cluster) level using binomial distribution with logit link function.
We will use robust standard errors for all outcomes to account for clustering. For participant-level outcomes we will use unweighted analysis while cluster-level outcomes will use weighted analysis (weight (1/cluster size).

Contingency measures for non-convergence of analysis models

Should any primary analysis models fail to converge covariates will be removed from the model using the hierarchical approach described in 4.1 If non-convergence persists after removing all covariates the alternative models described below will be used (starting with the full set of covariates). Analysis assumptions will be checked using appropriate methods (e.g., residual plots, overdispersion checks). IEE using GEE is robust to violation of assumptions. Only in case of severe violations or non-convergence will the following alternatives be used (in order):
For count outcomes:

- Negative binomial regression if overdispersion is present
- Zero-inflated models if excess zeros are observed

For binary outcomes:

- Generalized Linear Mixed Models (GLMM) with practice as a random effect.

For continuous outcomes:

- Transformation of the outcome variable
- Non-parametric methods

Any deviations from the planned IEE approach will be clearly reported and justified in the results, explaining why the alternative method was chosen and how it impacts on the interpretation of the estimand.

6.4 Missing data

Missing values at the individual level are likely to be extremely few in the routinely collected data due to the inclusion criterion of patients having to be on the practice 'active asthma' register at all three timepoints (i.e., eligible for the supported self-management intervention throughout the trial) extracted at 24 months after randomisation. Furthermore, many outcomes are clinical events where the presence of a relevant code in the EHR indicates the occurrence of the event. Absence of a code for such outcomes is assumed to be absence of an event in the time period rather than missing data. However, patterns and amount of missing data will be explored. The number and percentage of missing data on demographic questionnaires and, where applicable, clinical outcomes at baseline, 12 months, and 24 months post-randomisation will be summarised. Any known reasons for missing data will be described and discussed.

Where a whole cluster is missing because they fail to provide routine data via OPC, the values will be treated as missing for all participants in that cluster and at the cluster level. No imputation will be carried out.

QI-Q data sent to a proportion of participants is hypothesised to be missing not at random and will not be imputed.

6.5 Subgroup analyses

The following subgroup analyses will be performed for each variable separately. No multiple interaction terms will be included in a model and no higher order interactions assessed:

Variables for subgroup analysis

1. Age (<12, 13-24, 25-40 years, 40-65 years, >65 years) [patient level]
2. Gender (Male, Female) [patient level]
3. Risk of attacks [patient level] – steroid courses or unscheduled care in baseline period – using the categories
    1. 0 attacks

2. 1 attack/year
3. 2 attacks/year
4. 3 or more attacks/year

4. GINA control in baseline period (yes/no) [patient level]
5. Deprivation status (Low [lowest two quintiles], Medium [quintiles 3 &4], High [highest quintile] (based on Index of Multiple Deprivation))
6. Practice size (Small (<5000 patients), Medium (5000-10000 patients), Large (>10000 patients)
7. GP training status (Training practice, non-training practice).

Method of comparing subgroups

A likelihood ratio test of interaction effect comparing the primary analysis model, adding a main fixed effect for the subgroup variable if not previously included in the model, with the primary analysis model comprising additionally an interaction effect *allocation group x subgroup variable*.

Significance level

The significance level for interaction tests will be set at 0.05.

Outcomes for subgroup analysis

Primary clinical outcome: all subgroup analyses

Primary implementation outcome: Subgroup analyses for practice-level variables only

Descriptive statistics within subgroups:

Number and percentage of participants in each subgroup. Summary statistics for primary outcomes within each subgroup (e.g., mean, standard deviation, or proportion as appropriate). Forest plots to display treatment effects visually across subgroups. These subgroup analyses will only be performed on variables collected at baseline (in the baseline period) to avoid potential bias from post-randomisation factors.

6.6 Sensitivity analyses

The following sensitivity analysis will be performed to assess the robustness of the primary results:

Primary Clinical Outcome (Unscheduled Care):

Excluding code groups from outcome:

Repeat of the primary outcome analysis excluding from the outcome the groups of:

- steroid treatment codes
- imprecise codes (including emergency care admissions)
- both groups (precise codes only)

6.7 Complier-average causal effect (CACE) analysis

Practice-level fidelity to the components of the implementation strategy will be used to represent the categorical latent class variable (compliers vs. non-compliers). Fidelity to the IMP²ART implementation strategy is, by the nature of implementation, a complex spectrum of adoption/adaptation/attrition of a multi-component strategy. The process evaluation team reviewed the core components initially proposed for the implementation strategy and propose that four components should be used in the CACE analysis.

1. Workshop with at least one person present ('yes')
2. Practice received ≥20 monthly reports within three months of the month to it pertained ('yes')
3. Practice completed ≥80% of education Module 1 ('yes')
4. At least one person in the practice completed ≥80% of education Module 2 ('yes')

Appendix 8.2 provides details of all components which will be assessed individually and as an overall assessment of engagement with the implementation strategy. A practice is defined as an overall 'complier' if it satisfies (binary indicators status "yes") all four criteria otherwise the practice is overall a 'non-complier'.

CACE analysis will be performed with a latent variable approach (latent class variable 'compliance') using structural equation modelling. Stata's gsem command will be used with the same co-variates as the primary analysis model and bootstrap (n=100) standard errors. Deprivation status (IMD), practice training status, practices size and baseline period outcome prevalence will be used as predictors of the latent class compliance variable.

Should the modelling approach for the CACE analysis not be feasible a simpler approach proposed by Edwards et al (2025) will be used. The CACE point estimate would be calculated (not modelled) based on observed outcome prevalence and observed implementation group compliance. 95% CIs will be obtained from a bootstrapping approach accounting for clustering.

For the estimation of CACEs the following assumptions are made: 1) treatment assignment was random, 2) potential outcomes of each patient were not affected by the treatment status of other patients (the Stable Unit Treatment Value Assumption), 3) there are neither always-takers nor defiers, and 4) the treatment effect was zero for those who did not participate (exclusion criterion).

The 'dose-response' relationship will be explored by plotting and tabulating the primary clinical outcome by the number of compliance components a practice has completed (0-4) for intervention practices only.

6.8 Additional analyses

1. Cluster-Level Change from Baseline:

   We will conduct an additional analysis adjusting for the baseline period to assess the change from baseline in the primary clinical outcome.

   For each practice (cluster), we will calculate the baseline period proportion of the outcome measure This baseline proportion will then be added as a continuous cluster-level covariate to the primary outcome analysis model.

   Results will be presented as difference in proportion in change from baseline between groups, with 95% confidence intervals and p-values.

2. Analyse the primary clinical outcome as a count variable Unscheduled care in the period 12m to 24m post randomisation will be analysed counting the number of events in this period. A negative binomial distribution will be assumed for the outcome using the following analysis model to estimate the participant-average marginal mean difference in the expected counts:

   ```
   xtset practice
   xtgee outcome i.treat covariates, family(nbinomial) link(log)
   corr(independent) vce(robust) iterate(1000)
   margins r.group
   ```

   To ensure single events aren't double counted coded events need to be at least 2 weeks apart.

3. Assess consistency of GINA control in EHR with questionnaire data

6.9 Safety analysis

The IMP²ART trial utilises routinely collected practice-level electronic health record (EHR) data and does not include dedicated safety data collection. As such, no formal safety analysis will be conducted. The IMP²ART strategy aims to improve the implementation of evidence-based asthma self-management support, which is a recommended in clinical guidelines. Therefore, no additional safety risks are anticipated beyond those associated with standard asthma care.

6.10 Figures

The change over time of the primary clinical outcome and other binary outcome measures will be presented by treatment arm as figures showing the time point on the x-axis and the percentage on the y-axis.

7. References

1. IMPlementing IMProved Asthma self-management as RouTine (IMP2ART) in primary care: study protocol for a process evaluation within a cluster randomised controlled implementation trial. Trials. 2024;25(1):359. doi:10.1186/s13063-024-08179-6

2. Confederation BN. Investing in General Practice: The New General Medical Services Contract. In: ; 2003. https://api.semanticscholar.org/CorpusID:166568367
3. Pinnock H, Burton C, Campbell S, et al. Clinical implications of the Royal College of Physicians three questions in routine asthma care: A real-life validation study. Primary Care Respiratory Journal. 2012;21(3). doi:10.4104/pcrj.2012.00052
4. Mukherjee M, Stoddart A, Gupta RP, et al. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: Analyses of standalone and linked national databases. BMC Med. 2016;14(1). doi:10.1186/s12916-016-0657-8
5. British Lung Foundation. The Battle for Breath Report - The Impact of Lung Disease in the UK.; 2016.
6. Society BT, Network SIG. British Thoracic Society Scottish Intercollegiate Guidelines Network British guideline on the management of asthma A national clinical guideline. Thorax. 2014;69.
7. GINA. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2018. Presented at: 2018.
8. Chaplin S. Diagnosis, monitoring and management of chronic asthma. Prescriber. 2018;29(4). doi:10.1002/psb.1665
9. Pinnock H, Parke HL, Panagioti M, et al. Systematic meta-review of supported self-management for asthma: A healthcare perspective. BMC Med. 2017;15(1). doi:10.1186/s12916-017-0823-7
10. Gibson PG, Coughlan J, Wilson AJ, et al. Self-management education and regular practitioner review for adults with asthma. Praxis. 1999;88(39). doi:10.1002/14651858.cd001117
11. Gibson PG, Powell H. Written action plans for asthma: An evidence-based review of the key components. Thorax. 2004;59(2). doi:10.1136/thorax.2003.011858
12. Powell H, Gibson PG. Options for self-management education for adults with asthma. Cochrane Database of Systematic Reviews. 2002;2010(1). doi:10.1002/14651858.CD004107
13. Hodkinson A, Bower P, Grigoroglou C, et al. Self-management interventions to reduce healthcare use and improve quality of life among patients with asthma: Systematic review and network meta-analysis. The BMJ. 2020;370. doi:10.1136/bmj.m2521
14. Mccallum GB, Morris PS, Brown N, Chang AB. Culture-specific programs for children and adults from minority groups who have asthma. Cochrane Database of Systematic Reviews. 2017;2017(8). doi:10.1002/14651858.CD006580.pub5
15. Press VG, Pappalardo AA, Conwell WD, Pincavage AT, Prochaska MH, Arora VM. Interventions to improve outcomes for minority adults with asthma: A systematic review. J Gen Intern Med. 2012;27(8). doi:10.1007/s11606-012-2058-9
16. Postma J, Karr C, Kieckhefer G. Community health workers and environmental interventions for children with asthma: A systematic review. Journal of Asthma. 2009;46(6). doi:10.1080/02770900902912638
17. Chang AB, Taylor B, Masters IB, Laifoo Y, Brown ADH. Indigenous healthcare worker involvement for Indigenous adults and children with asthma. Cochrane Database of Systematic Reviews. 2007;(4). doi:10.1002/14651858.CD006344.pub2
18. Boyd M, Lasserson TJ, McKean MC, Gibson PG, Ducharme FM, Haby M. Interventions for educating children who are at risk of asthma-related emergency department attendance. Cochrane Database of Systematic Reviews. 2009;(2). doi:10.1002/14651858.CD001290.pub2
19. Bravata DM, Gienger AL, Holty JEC, et al. Quality improvement strategies for children with asthma: A systematic review. Arch Pediatr Adolesc Med. 2009;163(6). doi:10.1001/archpediatrics.2009.63
20. Kirk S, Beatty S, Callery P, Gellatly J, Milnes L, Pryjmachuk S. The effectiveness of self-care support interventions for children and young people with long-term conditions: A systematic review. Child Care Health Dev. 2013;39(3). doi:10.1111/j.1365-2214.2012.01395.x
21. Coffman JM, Cabana MD, Yelin EH. Do school-based asthma education programs improve self-management and health outcomes? Pediatrics. 2009;124(2). doi:10.1542/peds.2008-2085
22. Stinson J, Wilson R, Gill N, Yamada J, Holt J. A systematic review of internet-based self-management interventions for youth with health conditions. J Pediatr Psychol. 2009;34(5). doi:10.1093/jpepsy/jsn115
23. Baptist AP, Ross JA, Yang Y, Song PXK, Clark NM. A randomized controlled trial of a self-regulation intervention for older adults with asthma. J Am Geriatr Soc. 2013;61(5). doi:10.1111/jgs.12218

24. Goeman D, Jenkins C, Crane M, Paul E, Douglass J. Educational intervention for older people with asthma: A randomised controlled trial. Patient Educ Couns. 2013;93(3). doi:10.1016/j.pec.2013.08.014
25. Tapp S, Lasserson TJ, Rowe BH. Education interventions for adults who attend the emergency room for acute asthma. Cochrane Database of Systematic Reviews. 2007;(3). doi:10.1002/14651858.CD003000.pub2
26. Moudgil H, Marshall T, Honeybourne D. Asthma education and quality of life in the community: A randomised controlled study to evaluate the impact on white European and Indian subcontinent ethnic groups from socioeconomically deprived areas in Birmingham, UK. Thorax. 2000;55(3). doi:10.1136/thorax.55.3.177
27. Ducharme FM, Zemek RL, Chalut D, et al. Written action plan in pediatric emergency room improves asthma prescribing, adherence, and control. Am J Respir Crit Care Med. 2011;183(2). doi:10.1164/rccm.201001-0115OC
28. Marcano Belisario JS, Huckvale K, Greenfield G, Car J, Gunn LH. Smartphone and tablet self management apps for asthma. Cochrane Database of Systematic Reviews. 2013;2017(12). doi:10.1002/14651858.CD010013.pub2
29. Guidelines for management of asthma in adults: I--Chronic persistent asthma. Statement by the British Thoracic Society, Research Unit of the Royal College of Physicians of London, King's Fund Centre, National Asthma Campaign. BMJ. 1990;301(6753). doi:10.1136/bmj.301.6753.651
30. Hwang L. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2018. National Nurse. 2016;112(3).
31. Wiener-Ogilvie S, Pinnock H, Huby G, Sheikh A, Partridge MR, Gillies J. Do practices comply with key recommendations of the British Asthma Guideline? If not, why not? Primary Care Respiratory Journal. 2007;16(6). doi:10.3132/pcrj.2007.00074
32. Ställberg B, Lisspers K, Hasselgren M, Janson C, Johansson G, Svärdsudd K. Asthma control in primary care in Sweden: A comparison between 2001 and 2005. Primary Care Respiratory Journal. 2009;18(4). doi:10.4104/pcrj.2009.00024
33. Sulaiman N, Aroni R, Thien F, et al. Written asthma action plans (WAAPS) in Melbourne general practices: A sequential mixed methods study. Primary Care Respiratory Journal. 2011;20(2). doi:10.4104/pcrj.2011.00010
34. Newby C, Wright N, Eldridge S, et al. Estimating exacerbation rates from routine UK primary care data: an exploratory validation from the IMP2ART programme. In: ; 2017. doi:10.1183/1393003.congress-2017.pa1603
35. O'Kane R, Fay A. Why asthma still kills. Ulster Medical Journal. 2017;86(1).
36. Kennedy A, Rogers A, Bower P. Support for self care for patients with chronic disease. Br Med J. 2007;335(7627). doi:10.1136/bmj.39372.540903.94
37. Taylor SJ, Pinnock H, Epiphaniou E, et al. A rapid synthesis of the evidence on interventions supporting self-management for people with long-term conditions: PRISMS – Practical systematic RevIew of Self-Management Support for long-term conditions. Health Services and Delivery Research. 2014;2(53). doi:10.3310/hsdr02530
38. Pinnock H, Epiphaniou E, Pearce G, et al. Implementing supported self-management for asthma: A systematic review and suggested hierarchy of evidence of implementation studies. BMC Med. 2015;13(1). doi:10.1186/s12916-015-0361-0
39. Haahtela T, Tuomisto LE, Pietinalho A, et al. A 10 year asthma programme in Finland: Major change for the better. Thorax. 2006;61(8). doi:10.1136/thx.2005.055699
40. Souza-Machado C, Souza-Machado A, Franco R, et al. Rapid reduction in hospitalisations after an intervention to manage severe asthma. European Respiratory Journal. 2010;35(3). doi:10.1183/09031936.00101009
41. Shah SA, Quint JK, Sheikh A. Impact of COVID-19 pandemic on asthma exacerbations: Retrospective cohort study of over 500,000 patients in a national English primary care database. The Lancet Regional Health - Europe. 2022;19. doi:10.1016/j.lanepe.2022.100428
42. Davies GA, Alsallakh MA, Sivakumaran S, et al. Impact of COVID-19 lockdown on emergency asthma admissions and deaths: National interrupted time series analyses for Scotland and Wales. Thorax. 2021;76(9). doi:10.1136/thoraxjnl-2020-216380
43. Edwards T, Thompson J, Opondo C, Allen E. Practical inference for a complier average causal effect in cluster randomised trials with a binary outcome. *Clinical Trials*. 2025;0(0). doi:10.1177/17407745251378407

44. Pereira Macedo J, Agrinier N, Minary L, Kivits J, Giraudeau B Estimation of a risk difference in a cluster randomized trial,
Revue d'Épidémiologie. 2023, 71(2), doi.org/10.1016/j.respe.2023.101600.
45. Pinnock H, Burton C, Campbell S, Gruffydd-Jones K, Hannon K, Hoskins G, Lester H, Price D. Clinical implications of the Royal College of Physicians three questions in routine asthma care: a real-life validation study. *Prim Care Respir J* 2012; 21:288-94
46. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol. 2004;113:59–65. doi: 10.1016/j.jaci.2003.09.008

8. Appendices

8.1 Outcomes derivation

IMP²ART population selection

Definition:

All patients

- Registered at a participating practice 1 year before the randomisation date
- Still registered at that practice 2 years after the randomisation date
- With a coded diagnosis of asthma
- And prescribed an asthma medication in each year under study
- Aged 5 or over at the beginning of the baseline period data collection (i.e. aged 6 years or over at randomisation)
- Without "significant" COPD
    - (COPD diagnosis code and LAMA treatment)
- No records of biologics medication
- Not on the palliative care register.

Look up tables that are used can be found in the following folder in the BCC:

Z:/PCTU/HEALTH ECONOMICS/IMP2ART/Data/Lookups

The file names will be used in this description but also a pointer to which sheet of the attached Excel table we are referring to – for ease of use.

File Names	Excel sheet
Asthma diagnosis (SNOMED for asthma.csv)	**Asthma Diagnosis**
Unscheduled precise (unscheduled_precise.dta)	**Unscheduled care- precise**
Unscheduled imprecise (unscheduled_imprecise.dta)	**Unscheduled care – imprecise**
Steroids (steroid code list unscheduled care_VH check.xlsx)	**Steroids**

Ashtma_medications_and_costs (costofmed.rdata)	**Asthma medications**
Asthma_plan_read(asthma plan read.dta)	**Asthma Plans**
Asthma_plan_snomed(AP snomed.dta)	**Asthma Plans**
Palliative (/QOF_lists_2/QOF_palliative care_50.0_expanded_cluster_list_20250521.xlsx)	**QOF Palliative Care**
CHD (/QOF_lists_2/QOF_chd_50.0_expanded_cluster_list_20250521.xlsx)	**QOF CHD**
Diabetes (/QOF_lists_2/QOF_diabetes_50.0_expanded_cluster_list_20250521.xlsx)	**QOF Diabetes**
Hypertension (/QOF_lists_2/QOF_Hypertension_50.0_expanded_cluster_list_20250521.xlsx)	**QOF Hypertension**
COPD (/QOF_lists_2/QOF_copd_50.0_expanded_cluster_list_20250521.xlsx)	**QOF COPD**
Biologics (SNOMED codes biologics.xlsx)	**Biologics**
COPD meds (all medications vHP.xls)	**COPD medications**

Steps

1. In therapy data set create flags for asthma medications, steroid use, biologics, COPD medications
2. In clinical data set, create flag for asthma diagnosis, COPD, palliative care, CHD, diabetes, hypertension, asthma action plans
3. In clinical data set, flag unscheduled care using precise codes, imprecise codes + steroids (within one day either way), number of exacerbation codes (this can be kept or deleted depending on outcome of our meeting)
4. Join all data sets back together and delete all records where patients were not registered at the practice for the study duration
5. Delete all under 5s

6. Delete all who do not have an asthma diagnosis code ever
7. Delete all who do not have "active asthma"
8. Delete all who have prescription of biologics (implying under the care of severe asthma clinic)
9. Delete all who have severe copd (copd diagnosis and prescription of COPD medication
10. Delete all who are on the palliative care register

Final data is saved to Excel file *Active asthma v0.20*

8.2 Fidelity categories (complier definition)

Component *[Target]*	Engagement criterion (n*)	Did not engage	*[Equation]* Notes
Facilitation *[Pivotal/over-arching]*	Workshop with at least one person present (n=65)	No workshop	'Plan B' practices did not receive a workshop, although one had some contact
Audit and feedback *[Organisational]*	Practice received ≥20 monthly reports within three months of the month to it pertained (n≈36)	Practice received <20 monthly reports within three months of the month to it pertained	*[Number of reports delivered within 3-months of the month to which they pertained]/24* From process evaluation data: • Practices received between 10-24 reports with <3m delay (median 22). • 20 is 83% of possible 24 reports.
Education module-1 *[Professional (team)]*	Practice completed ≥80% of Module 1 (n≈58)	Practice did not complete ≥80% of Module 1	• Module-1 is team-based learning; log-in was at practice level. • 80% is widely used as a threshold for completion of e-learning modules.
Education module *[Professional (individual)]*	At least one person in the practice completed ≥80% of Module 2 (n≈52)	No-one in the practice completed ≥80% of Module 2	• Module-2 is designed for individual learning by the clinician responsible for asthma care (though available for all practice clinicians); log-in was at individual level. • 80% is widely used as a threshold for completion of e-learning modules. • The process evaluation has descriptive data about how many/how much and which professional groups completed Module 2
Template *[Organisational]*	• We have download stats (n=47), but data on whether the practice actually used the IMP²ART template is incomplete		• Arderns template use was incentivised by health boards overriding IMP²ART
Living with asthma website	• We have overall Google analytics, but not by practice, and cannot distinguish patient/professional usage		• Implementation practices given access to LwA website which

[Patient and professional]			included patient-facing information as well as professional resources
Complier definition composite			
Overall engagement with IMP²ART	Practice satisfies the four components Facilitation, Audit and feedback, Team module-1, Education module-2	Practice did not satisfy all four components	We could make this dose related. Practices engaging with 1, 2 , 3 or 4 components

8.3 CONSORT 2010 Flow diagram