Title {1a}

The **C**anadian **AN**tibiotic prescribing feedback initiation: **Build**ing a national framework to combat **A**nti**M**icrobial **R**esistance in primary care (CANBuild-AMR): study protocol for a comparative effectiveness randomized controlled trial

Names of protocol contributors {3a}

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Trial registration

ISRCTN. *ISRCTN90477957*. Registered 04 November 2025

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Abstract

Background:

Antimicrobial resistance is a growing global public health threat, largely driven by the misuse and overuse of antibiotics. In the community, where over 90% of human antibiotics are

prescribed, up to half are unnecessary. Peer comparison audit and feedback improve prescribing, but it is unclear which type of feedback data most effectively reduces unnecessary antibiotic prescribing. The trial aims to assess whether providing primary care physicians with feedback on unnecessary antibiotic initiations improves prescribing more than standard feedback on overall prescribing rates.

Methods:

This comparative effectiveness research study will use a parallel group, RCT design. Primary care physicians in Ontario caring for patients aged ≥65 will be randomized 1:1 to receive feedback on either unnecessary antibiotic initiations or overall prescribing rates. Physicians will be excluded if they work <44 days/year, prescribe <10 antibiotics/year, have <100 patient visits or <6 visits for a viral respiratory infection in the target population in the most recent year or ≥2 out of the last 3 years or have opted out of our previous letter. All other eligible physicians will be automatically enrolled.

The intervention will provide feedback on either unnecessary initiation or overall prescribing rates. Feedback on unnecessary initiation may be more actionable and link more directly to desired behaviour change, though may be less accepted by prescribers. The primary outcome will be the relative difference in antibiotic prescribing rate between groups (total prescriptions per 1,000 patient visits for patients ≥65) measured 6 months post-intervention (anticipated to be December 2025 to May 2026). The secondary outcome will be the proportion of prescriptions considered unnecessary. Our power simulations indicate that a sample size of 8,000 physicians (4,000 per arm) will provide 93% power to detect a 2.5% relative change in the primary outcome. Analyses will follow a modified intention-to-treat principle using routinely collected administrative data and analyzed using Poisson regression models.

Discussion:

This study will generate evidence to optimize antibiotic prescribing feedback for primary care providers, supporting scalable interventions within existing infrastructure. Findings will inform policy and practice to reduce unnecessary antibiotic use and address AMR in the community.

Trial registration:

ISRCTN90477957. Registered on 04 November 2025. This trial was prospectively registered (before letter distribution). https://doi.org/10.1186/ISRCTN90477957.

Keywords: Audit and feedback, antibiotic stewardship, primary care, antibiotic prescribing, antimicrobial resistance, process evaluation, protocol, peer comparison

Structured summary {1b}

Item	**Description**
Primary Registry and Trial Identifying Number {4}	ISRCTN90477957. Registered on 04 November 2025. This trial was prospectively registered (before letter distribution). https://doi.org/10.1186/ISRCTN90477957.
Secondary Identifying Numbers	N/A
Source(s) of Monetary or Material Support	Monetary Support: The Canadian Institutes of Health Research (CIHR) Material Support: The study is managed by PHO, using data from ICES, a research institute in Ontario that collects

	and links health information for system evaluation.
Primary Sponsor and contact information {3b}	PHO Email: research@oahpp.ca Address: 661 University Avenue, Suite 1701, Toronto, M5G 1M1, Canada
Role of sponsor and funder {3c}	Sponsor: PHO Funder: CIHR
Contact for Public Queries	Kalisha Ramlackhan Phone: +1 647-792-3605 Email: kalisha.ramlackhan@oahpp.ca
Contact for Scientific Queries	Kevin Schwartz Phone: +1 647-260-7629 Email: Kevin.Schwartz@oahpp.ca
Public Title	CANBuild-AMR
Scientific title	The Canadian ANtibiotic prescribing feedback initiation: Building a national framework to combat AntiMicrobial Resistance in primary care: study protocol for a comparative effectiveness RCT
Countries of Recruitment	Canada
Health Condition(s) or Problem(s) Studied	Antimicrobial stewardship in primary care through the prevention of unnecessary antibiotic prescribing for viral respiratory infections among older adult

	patients (aged ≥65 years) in Ontario, Canada
Intervention(s)	A single mailed, personalized peer-comparison antibiotic prescribing feedback letter with unnecessary antibiotic prescribing metric. The control group will also receive a single mailed, personalized peer-comparison antibiotic prescribing feedback letter with total antibiotic prescribing rate metric.
Key Inclusion and Exclusion Criteria	Inclusion - Primary care physician (family medicine or general practitioner) in Ontario, Canada Exclusion - Inactive physician, defined as working less than 44 days per year - Prescribed fewer than 10 antibiotic prescriptions to patients aged 65 years and older in the most recent year or 2 out of the last 3 years - Fewer than 100 outpatient visits with patients aged 65 years or older in the most recent year or 2 out of the last 3 years - Fewer than 6 outpatient visits for a viral

	respiratory infection with patients aged 65 years or older in the most recent year or 2 out of the last 3 years - Physicians who previously opted out after receiving antibiotic prescribing feedback letters
Study Type	Two-arm, parallel-group RCT; 1:1 allocation; no blinding of participants (mailed letters); modified intention-to-treat analysis; superiority framework
Date of First Enrollment (planned)	December 2025
Sample Size	8,000 physicians (4,000 intervention, 4,000 control)
Primary Outcome	Antibiotic prescribing rate measured using routinely collected administrative health data at 6 months post-intervention
Key Secondary Outcomes	1. Proportion of unnecessary antibiotic prescriptions measured using administrative health data at 6 months post-intervention, percentage of antibiotics prescribed for viral respiratory infections without bacterial codes in patients aged 65 years and older 2. Diagnostic code switching measured using administrative health data at 6 months post-

	intervention, proportion of respiratory infection codes where antibiotics are not indicated relative to all respiratory infection codes
Ethics Review	PHO's Ethics Research Board (REB# 2024-017.02) Address: 661 University Avenue, Suite 1701, Toronto, M5G 1M1, Canada Phone: +1 416-235-6556 Email: ethics@oahpp.ca Original ethics approval document included in Supplementary Material.
Individual Trial Participant Data Sharing Statement	Participant-level data from ICES cannot be publicly shared due to legal/data agreements. Aggregate tables and de-identified analytic code will be made available upon reasonable request. Researchers may contact ICES Data & Analytic Services (das@ices.on.ca) for access under ICES policies.

Protocol version {2}

Version 1.0 - 17 Dec 2025.

Introduction

Background and rationale {9a}

Global and national threat of antimicrobial resistance

Rising antimicrobial resistance (AMR) poses a threat to the practice of medicine and to society. In 2019, more than 1.2 million global deaths were attributable to bacterial AMR (1). Inappropriate use of antibiotics is an essential contributor to this health crisis. National actions are necessary to slow AMR and avoid a post-antibiotic era where bacterial infections are no longer treatable. One of the pillars of the Pan-Canadian Action Plan on AMR is to optimize antibiotic use in humans (2).

Importance of primary care in antimicrobial stewardship

While antimicrobial stewardship efforts have historically focused on hospitals due to a more captive audience of prescribers and accreditation requirements (3), approximately 90% of antibiotic use occurs in the community, making primary care a critical partner for stewardship initiatives (4,5). It is estimated that 25-50% of antibiotics prescribed in primary care in high-income countries are unnecessary (6–8). In particular, antibiotic prescriptions for respiratory tract infections are often inappropriate. Canadian studies have shown that up to 50% of these prescriptions are given for upper respiratory viral infections, offering no benefit to patients while increasing the risk of adverse effects and AMR (9,10). Substantial variability in antibiotic prescribing across and within provinces further highlights opportunities for improvement (9,11).

Evidence for peer comparison audit and feedback

Effective antimicrobial stewardship programs in primary care are essential. These programs should be multifaceted and grounded in behavioural science. Peer comparison audit and feedback (A&F) is an evidence-based strategy that can reduce unnecessary antibiotic prescribing at the population level (12–15). A previous mailed feedback intervention in Ontario led to a 5% relative reduction in overall antibiotic use and an 8% reduction in prolonged duration of

prescription. The cost of the intervention was approximately $135,000, and enabled an estimated $2.7 million in drug cost savings over the first 12 months (12,13).

Current audit and feedback infrastructure for primary care physicians in Ontario

Ontario Health (OH), a publicly funded provincial agency responsible for connecting and coordinating Ontario's healthcare system, provides A&F reports to primary care physicians through the "MyPractice: Primary Care" initiative. Approximately half (4,750 out of 9,500) of family physicians in Ontario are voluntarily enrolled in the program. These multi-topic reports are sent twice a year through email to enrolled physicians to access an electronic dashboard. As of December 2021, the reports include antibiotic prescribing metrics and links to educational materials, including Choosing Wisely Canada tools such as the viral prescription pad (14). The antibiotic prescribing metrics include the overall antibiotic prescribing rate (APR) in patients 65 years of age and older and the proportion of prolonged duration prescriptions.

Previous interventions and rationale for the current study

Since 2022, in parallel with electronic, voluntary MyPractice reports, Public Health Ontario (PHO) has mailed peer comparison feedback letters on total APR for patients 65 years of age and older and prolonged duration prescribing to all eligible primary care physicians, as part of either a randomized trial or operational antimicrobial stewardship interventions. The goal of this joint program is to improve engagement with A&F, particularly for physicians who have not voluntarily signed up to receive MyPractice reports. We have previously demonstrated that providing antibiotic prescribing feedback on older patients improves prescribing by these physicians to patients of all ages (15).

Optimizing effectiveness of feedback interventions

Optimizing the effectiveness of feedback interventions is key to reducing unnecessary prescribing. Feedback is more effective when delivered by a credible source and when it clearly links prescribing metrics to the desired behaviour change (16–18). In Ontario, Canada we have previously used total antibiotic prescribing as a proxy for inappropriate use, which is reasonable in settings with high baseline overprescribing (6,10). Some studies have used direct measures of inappropriate prescribing, such as prescribing for viral infections, which may be more actionable for physicians. This, however, requires access to diagnostic data, which can be challenging to access and may suffer from lower face validity if based on billing codes (18,19). The trade-offs between these two approaches remain unclear, and a direct comparison has not previously been made.

CANBuild-AMR collaboration

This study is being conducted as part of the **C**anadian **AN**tibiotic prescribing feedback initiation: **Build**ing a national framework to combat **A**nti**M**icrobial **R**esistance in primary care (CANBuild-AMR). CANBuild-AMR is a national collaboration with the goal of building capacity, and expanding the evidence base, through nation-wide antibiotic prescribing feedback in primary care.

Explanation for the choice of control {9b}

The control group receives peer-comparison feedback based on the overall APR. This was chosen as the control because APR feedback represents the standard approach used in previous A&F initiatives in Ontario. We have previously demonstrated that using this metric, compared to a control group that received no feedback, is effective at reducing antibiotic use (13). Comparing UAP-based feedback to APR-based feedback allows evaluation of whether focusing on unnecessary prescribing provides different improvements in prescribing behaviour than overall

prescribing metrics, while ensuring that all physicians receive actionable stewardship information.

Objective {10}

This trial will evaluate whether providing feedback to primary care physicians in Ontario on unnecessary antibiotic prescribing (UAP) rates for viral respiratory conditions results in different changes in overall and unnecessary antibiotic prescribing compared with providing feedback on overall prescribing rates (APR). Understanding which strategy is more effective will help shape future antimicrobial stewardship efforts and guide best practices for A&F.

Methods: Patient and public involvement, and trial design

Patient and public involvement {11}

Patients were not directly involved in the design, conduct, or reporting of this trial. The intervention targets primary care physicians, and patient outcomes are measured only through routinely collected administrative data. No patient-facing procedures are included, and no additional burden or risk is imposed on patients.

Trial design {12}

This comparative effectiveness research (CER) study uses a parallel group, randomized controlled trial (RCT) design. The trial compares two types of peer-comparison A&F delivered to primary care physicians: UAP feedback (intervention) versus APR feedback (control). The trial is designed with a superiority framework, aiming to determine whether UAP-based feedback is more or less effective than APR-based feedback in reducing antibiotic prescribing. Each physician will be randomized to one of two groups: one group will receive feedback on their total APR, expressed as total number of antibiotic prescriptions per 1,000 patient visits; the

other will receive feedback on their UAP, expressed as a percentage of viral respiratory visits where an antibiotic was prescribed. This RCT will compare these two groups in terms of their antibiotic prescribing patterns (both APR and UAP) at 6 months following the intervention.

Protocol information

This protocol was prepared in accordance with the SPIRIT 2025 Statement for clinical trial protocols. A completed SPIRIT checklist is provided as Additional file 1 (21).

Methods: Participants, interventions and outcomes

Trial setting {13}

This study will be conducted in Ontario, Canada's most populous province (population in 2025 approximately 16 million), which operates a publicly funded healthcare system as required by the Canada Health Act. This system provides universal coverage for all medically necessary physician visits and procedures (22).

The study population consists of all actively practicing primary care physicians, including family medicine and general practitioners, within Ontario, Canada. Physicians that have signed up for electronic MyPractice reports will also receive a mailed letter if otherwise eligible. The randomization will be stratified by whether physicians have signed up for these reports or not. A PICOT description for this trial is provided in Table 1. Participant characteristics are summarized in Table 2, following PRO EDI guidance.

Table 1. PICOT Table of Ontario's A&F RCT

Population	Actively practicing primary care physicians in Ontario, Canada who

	prescribe antibiotics to patients aged 65 years or older.
Intervention	A single mailed personalized peer-comparison antibiotic prescribing feedback letters with UAP for viral respiratory conditions.
Comparison	Personalized peer-comparison mailed antibiotic prescribing feedback letters with overall APR.
Outcome	Primary Outcome: APR defined as the total number of antibiotic prescriptions per 1,000 patient visits 65 years of age or older. Secondary Outcomes: UAP defined as the proportion of antibiotic prescriptions that are considered unnecessary. Code switching will be calculated as the proportion of prescriptions for

	unnecessary prescribing codes relative to all respiratory infection codes.
Time	6 months following the intervention.
Abbreviations: APR=total number of antibiotics prescriptions; UAP=proportion of antibiotic prescriptions that are considered unnecessary.	

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230 **Table 2. Demographic characteristics of trial participants**

Characteristic	**The people we would expect to see included**
Age	Primary care physicians, adults across a wide range of ages (no minimum or maximum age).
Patient sex	Sex of patients within each physician's practice is collected and will be summarized as physician - level baseline characteristic (e.g., proportion of patients who are male/female).
Physician gender	Physician gender is collected and included as a covariate in analyses (e.g., male/female).
Race, ethnicity and ancestry	Not collected.

Socioeconomic status	Practice-level SES is included: neighbourhood income quintile of the physician's practice location (used for equity analyses).
Geographic location	Physicians practicing in Ontario, Canada (physician clinic address)**.** Analyzes consider rural vs. urban practice location.
Other characteristics relevant to the trial	- Physician years in practice - Patient volume - Baseline antibiotic prescribing rates - Enrollment status in MyPractice reports

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232 **Data sources**

233 The study will utilize administrative, real-world health data linked from ICES databases. ICES
234 (formerly, The Institute for Clinical Evaluative Sciences) holds administrative health services
235 records for individuals in Ontario who are eligible for universal health coverage (≈ 98.5% of the
236 total Ontario population). ICES can therefore link prescriber characteristics, including patient
237 volume, and patient characteristics, to prescription dispensing data. The drug data are >99%
238 accurate but complete only for patients 65 years of age and older (23).

239 **Eligibility criteria for participants {14a}**

240 **Inclusion criteria**

The study inclusion criteria include general/family medicine practice in the ICES Physician Database. Eligible physicians will be automatically enrolled into the trial unless they have previously opted out of antibiotic A&F from PHO (n=70).

Exclusion criteria

Exclusion criteria include: inactive physicians (defined as working <44 days/year), physicians who prescribed <10 antibiotic prescriptions to patients aged 65 years or older in the most recent year or 2 out of the last 3 years, physicians with <100 outpatient visits with patients aged 65 years or older in the most recent year or 2 out of the last 3 years, physicians with <6 outpatient visits for a viral respiratory infection with patients 65 years or older in the most recent year or 2 out of the last 3 years and physicians who opted out after receiving previous antibiotic feedback letters (n=70 physicians). See Additional file 2 for the definitions of viral respiratory infections.

Who will take informed consent? {32a}

Informed consent is not required for trial participation. The Research Ethics Board approved a waiver of informed consent for this trial. Physicians are automatically enrolled unless they have previously opted out of receiving A&F letters.

Additional consent provisions for collection and use of participant data and biological specimens {32b}

No consent provisions are required because no biological specimens are collected and all data originate from de-identified administrative databases accessed under ICES' legal data provisions.

Intervention and control

Intervention and control description {15a}

Intervention overview

The feedback will be provided through a personalized, single-mailed letter, to physicians primary clinic address, sent by a blinded printing/mailing vendor. Both groups (intervention and control) will have a peer comparison of the 25th percentile since the average Ontario physician can safely reduce antibiotic prescribing by at least 25% (6). Antibiotic A&F should avoid providing the mean as a comparison to optimize impact and avoid regression to the mean (22). The intervention description was developed using the Template for Intervention Description and Replication Checklist (24), provided in Additional file 3.

All eligible physicians will receive a mailed letter to their primary care practice address, in a confidential envelope. The letter will outline their personalized antibiotic prescribing patterns and include other educational resources. The intervention design incorporates best practices of A&F utilizing principles of behavioural science (25).

We built on previous successful interventions that resulted in modest reductions in antibiotic prescribing and included components of social comparison, instruction on how to perform the behaviour, and education on appropriate antibiotic initiation and duration (12,26,27). The feedback letters were developed through a rigorous, iterative process involving extensive stakeholder engagement and contributions from the CANBuild-AMR intervention working group, which includes experts in A&F, primary care, and infectious diseases.

Development process

We conducted one-on-one interviews with nine primary care physicians across multiple Canadian provinces, including Ontario, British Columbia, and Nova Scotia, employing a user-centered design approach. Insights and themes from these interviews were systematically summarized and presented to the intervention working group established for this research. The

intervention was then refined in successive iterations to enhance clarity while preserving the core behavioural science principles essential for optimizing A&F effectiveness (22). Patients were not directly involved in designing the trial.

Letter signatories

Several prominent provincial and national organizations are planned to be signatories on the feedback letters including the chair of Choosing Wisely Canada, Ontario's Chief Medical Officer of Health, and the president of the Ontario College of Family Physicians.

Intervention versions

Each participating physician will receive one of four versions of a feedback letter. All four versions of the letter will contain four pages and share identical content on pages two through four. The content of the first page varies according to (1) randomized assignment to the control group (feedback on overall antibiotic prescribing rates) or intervention group (feedback on unnecessary antibiotic prescribing for viral respiratory conditions) and (2) the physician prescribing performance relative to a predefined peer-comparison benchmark, the *achievable target*. Physicians performing above or below the achievable target receive minor, performance tailored wording differences on the first page. See supplementary material (Additional files 4–7) for letter versions. All letters will include a link and QR code to an online appendix with additional information and definitions, as well as an opportunity to opt out of receiving future A&F letters. Physicians also can provide feedback on the letter directly to the project research team.

Intervention timeline

The intervention is planned to be initiated in December 2025, with outcome assessment completed at 6 months (June 2026). A debrief letter with updated prescribing feedback will be

sent to all physicians by a blinded vendor, in the control and intervention groups 12 months later (December 2026).

Intervention group

The intervention group will receive a single mailed antibiotic prescribing feedback letter, with peer comparison, using the UAP data metric (Additional files 4 and 5).

Control group

The control group will receive a single mailed antibiotic prescribing feedback letter, with peer comparison, using the APR data metric (Additional files 7 and 8).

Criteria for discontinuing or modifying allocated intervention/control {15b}

All eligible physicians will be automatically enrolled in the trial unless they have previously opted out of receiving antibiotic A&F letters from PHO (n=70). No other criteria for discontinuing or modifying the allocated intervention exist, as the intervention consists of a single mailed feedback letter and does not involve ongoing treatment or procedures.

Strategies to improve adherence to intervention/control {15c}

All physicians will receive the intervention or control letter automatically at their primary care practice address. Fidelity of delivery is ensured through standardized mailing procedures, including pre-specified letter templates and centralized processing. No additional procedures are planned to monitor participant adherence, as it is not possible to determine whether letters are received, opened, or engaged with directly. The intervention is a single informational communication, and adherence is therefore assumed based on standard delivery.

Concomitant care permitted or prohibited during the trial {15d}

We cannot measure whether letters were received or opened by participants, nor directly measure engagement with feedback. Concomitant care or other quality improvement activities during the

study period will not be systematically tracked. No formal trial monitoring visits are planned because the intervention is minimal and all outcomes come from administrative databases.

Ancillary and post-trial care {34}

Not applicable. This study does not involve patient-level clinical procedures, and no health-related harm is anticipated from receiving or not receiving mailed A&F materials.

Outcomes {16}

Primary outcome

We selected APR as the primary outcome as it is the objective and accurately captured with administrative data for the study population. APR is defined as the total number of antibiotic prescriptions per 1,000 patient visits for patients aged 65 years or older. This outcome will be assessed 6 months post-intervention (December 2025 to June 2026) between the intervention and control groups. We will report the number of physicians included in the analysis for each trial arm.

Secondary outcomes

For secondary outcomes, we will similarly report the number of physicians analyzed and the results by trial arm. Both absolute and relative effect sizes will be presented with corresponding 95% confidence intervals. Secondary outcomes will be measured and will use previously defined definitions (6,26,28):

- UAP defined as the proportion of antibiotic prescriptions that are considered likely unnecessary (Additional file 3). This outcome was chosen as secondary, since physicians could potentially change their billing practices to change the denominator (e.g., code as pneumonia instead of acute bronchitis).

- To monitor for any change in billing practices we will also assess for a change in use of respiratory infection codes as another secondary outcome, defined as the proportion of codes for respiratory conditions where antibiotics are not indicated as used in the UAP metric, out of all respiratory infection codes (Additional file 3). This outcome will assess physicians' changing coding practices based on the feedback metric received. A comparative increase in this secondary outcome would suggest an increase in antibiotic rationalization.

Outcome denominators and calculations

The denominator for the UAP outcome includes visits for viral respiratory conditions among patients aged ≥65 years. Codes listed under "other respiratory infections" will be used in the denominator for the secondary outcome assessing code switching. Antibiotic prescriptions for these viral conditions are considered inappropriate if issued within three days without any diagnostic code suggesting a bacterial infection. Code switching will be calculated as the proportion of prescriptions for unnecessary prescribing codes relative to all respiratory infection codes. Definitions and calculations for APR, UAP, and prolonged duration are detailed in Additional file 3.

Harms {17}

There are no foreseeable harm or risks anticipated from modifying the data metric used for antibiotic prescribing feedback letters to physicians. No formal adverse event reporting procedure for physicians is planned. Physicians may opt out of receiving future feedback letters through the link included in the mailed letter.

Table 3. Participant timeline {18}

Phase	**Time Period**	**Activity**
Enrolment	October to November 2025	- Identify eligible physicians using ICES administrative data. - Remove past opt-out requests prior to allocation.
Randomization	November 2025	- Random allocation of physicians to intervention or control groups.
Intervention	December 2025	- Mail A&F letters to enrolled physicians (clinic address).
Outcome Assessment Window	December 2025 to June 2026	- Primary Outcome: APR defined as the total number of antibiotic prescriptions per 1,000 patient visits 65 years of age or older. - Secondary Outcome: UAP defined as the proportion of antibiotic prescriptions that are considered unnecessary.

		- Code switching will be calculated as the proportion of prescriptions for unnecessary prescribing codes relative to all respiratory infection codes.
Post-trial / Debriefing	December 2026	- Provide high-level results summary. - Debrief to participating physicians.

Sample size {19}

Our power simulations indicate that a sample size of 8,000 physicians (4,000 per arm) will provide 93% power to detect a 2.5% relative change in the primary outcome.

Recruitment {20}

Recruitment is automatic through the standard mailing process: all eligible physicians will receive a personalized feedback letter at their primary care practice address. This approach ensures comprehensive coverage of the target population and is expected to achieve the planned sample size of approximately 8,000 physicians. No additional recruitment strategies are required due to the use of population-wide administrative data for enrollment.

Assignment of interventions: randomization

Sequence generation: who will generate the sequence {21a}

Randomization sequences will be generated centrally using a computer-based random generator.

Sequence generation: type of randomization {21b}

This study will be a two-arm parallel trial, and randomization will occur on a 1:1 basis. We will use a simple random sampling method without replacement and with no block size specification or clustering. The unit of randomization is the physician. Randomization sequences will be generated centrally using ICES administrative data, with stratification by MyPractice enrollment.

Allocation concealment mechanism {22}

There will be no allocation concealment or blinding of participants. Physicians will not be informed they are in a trial and will not have access to data for the other group. Although physicians practicing within the primary care setting may discuss he feedback letters, the risk of contamination is expected to be limited, as letters are individually addressed, contain physicians specific prescribing data, and do not disclose assignment or comparative data beyond the achievable target.

Implementation {23}

Trial arm assignments will be implemented automatically by an independent analyst who is not otherwise involved in the study.

Assignment of interventions: blinding

Who will be blinded {24a}

Given the nature of the intervention, mailed A&F letters, participants cannot be blinded; however, outcome data are collected independently in administrative databases, and statistical analysts will remain blinded to group assignments to reduce the risk of bias.

How will be blinding be achieved {24b}

Blinding of statistical analysts will be maintained by providing de-identified data with intervention groups labeled.

Procedure for unblinding if needed {24c}

Not applicable as participants are not blinded.

Methods: study flow

Participant enrolment, allocation, follow-up, and analysis will be documented using a CONSORT 2025 flow diagram. The planned CONSORT flow diagram and completed CONSORT 2025 checklist are provided in Additional file 4.

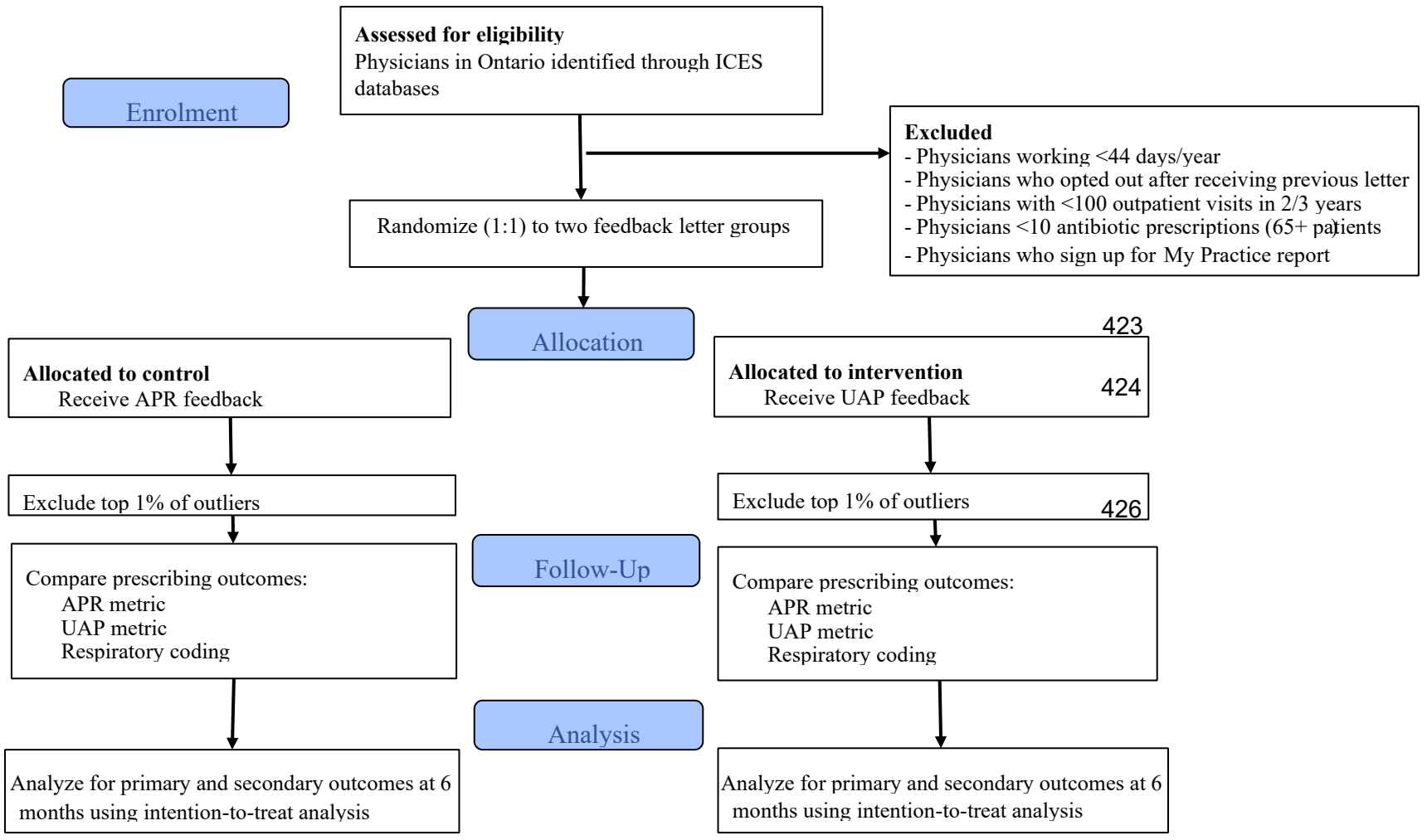
Enrolment
Assessed for eligibility
Physicians in Ontario identified through ICES databases
Excluded
- Physicians working <44 days/year
- Physicians who opted out after receiving previous letter
- Physicians with <100 outpatient visits in 2/3 years
- Physicians <10 antibiotic prescriptions (65+ patients)
- Physicians who sign up for My Practice report
Randomize (1:1) to two feedback letter groups
Allocation
Allocated to control
Receive APR feedback
Allocated to intervention
Receive UAP feedback
Exclude top 1% of outliers
Exclude top 1% of outliers
Follow-Up
Compare prescribing outcomes:
APR metric
UAP metric
Respiratory coding
Compare prescribing outcomes:
APR metric
UAP metric
Respiratory coding
Analysis
Analyze for primary and secondary outcomes at 6 months using intention-to-treat analysis
Analyze for primary and secondary outcomes at 6 months using intention-to-treat analysis

Figure 1 CONSORT flow diagram for trial. CONSORT flow diagram illustrates the anticipated flow of eligible primary care physicians through each phase of the RCT including enrolment, intervention, allocation, follow-up and data analysis (20).

Sample size / power calculation

We conducted a simulation study to estimate power. First, we directly estimated (from our previous trial (8) baseline APR, interphysician variation in baseline APR, and the number of patient visits. Next, we simulated a trial with these parameters with 8,000 physicians (4,000 in the intervention group, 4,000 in the control group), and a baseline APR of 100 per 1,000 visits. We simulated interphysician variation in baseline prescribing rates as a lognormal distribution; mean=98, standard deviation (SD)=0.66 on the natural log scale (corresponding to an ICC of 0.18**;** APR distribution: p10=31, median=76, p90=188). Similarly, we simulated annual patient visits as a lognormal distribution; mean=1257 and SD=1 on the natural log scale (yielding a visit distribution: p10=326, median=910, and p90=2530). We set the correlation between the baseline APR and the intervention period APR to 0.8. We then simulated 10,000 trials. Assuming an intervention effect equal to a rate ratio (RR) of 0.975, we estimated the power to be 93%.

Data collection and management

Plans for assessment and collection of outcomes {25a}

The data for all outcomes were derived from routinely collected administrative data at ICES. The data to measure prescribing quality indicators in the feedback letters and the outcomes will be sourced from several administrative health data sources at ICES. The Ontario Drug Benefit (ODB) plan, funded by the province, offers coverage without co-payments for most medications, including commonly prescribed antibiotics. The ODB database includes specific groups, such as

individuals aged 65 years and older, and has been shown to have an accuracy rate exceeding 99% (23).

Additional ICES datasets will be linked to providing information on diagnostic codes, patient demographics, and physicians characteristics. The Ontario Health Insurance Plan database to track physician visits; the Registered Persons Database to obtain patient demographic details; the Canadian Institute for Health Information Discharge Abstract Database is used to identify hospitalizations; the Continuing Care Reporting System will identify patients residing in a Long-Term Care Home; and the ICES Physician Database to capture information on prescriber characteristics. These datasets will be linked using unique encoded identifiers and analyzed at ICES.

Plans to promote participant retention and complete follow-up {25b}

Given that all outcome data are derived from routinely collected administrative databases, active participant retention strategies are not required.

Data management {26}

All data management, including data entry, coding, security, storage, and quality checks, will be performed within the secure ICES and PHO environments. Physician-level antibiotic prescribing data will be de-identified prior to analysis, and unique Study IDs will be assigned for tracking. Data quality will be promoted through automated consistency and range checks. Randomization and outcome analyses will be performed by ICES staff independent of the intervention delivery. Secure data transfer between ICES, PHO, and authorized collaborators will follow standard protocols, including restricted access and audit trials.

Confidentiality {33}

All data used in this study are derived from routinely collected administrative health databases held securely at ICES. These datasets contain coded, de-identified information, and ICES links them using unique encoded identifiers. All data management, storage, and security procedures follow ICES' established confidentiality and privacy processes. No identifiable information is available to the research team.

Statistical analysis

Statistical methods for primary and secondary outcomes {27a}

Baseline characteristics of participating physicians including gender, years in practice, patient volume, baseline prescribing rates, will be summarized by trial arm using descriptive statistics. The intervention period will be 0–6 months after the letter is sent.

The primary analysis will compare the intervention group versus the control group using Poisson regression with observation-level random intercepts corresponding to the physician (29). The dependent variable will be the number of antibiotic prescriptions offset by the log of the number of patient visits. The models will adjust for the natural logarithm of the baseline prescribing rate, defined as prescriptions per patient visit over the 12 months prior to the intervention (i.e., November 2024 to November 2025). Additional covariates include physician gender, years in practice, and whether the physician has signed up for MyPractice reports, which served as the stratification variable for randomization. These variables will be included in the model to optimize power. The significance level (alpha) for all primary analysis is pre-specified at 0.05. Both absolute and relative effect sizes will be presented with corresponding 95% confidence intervals.

Who will be included in each analysis {27b}

The data will be analyzed as modified intention-to-treat using administrative data held at ICES. The highest 1% of outliers, based on baseline APR, will be excluded, after randomization, to minimize data errors from implausibly high prescribing numbers attributed to a small number of physicians similar to our previous trial (26).

How missing data will be handled in the analysis {27c}

We anticipate minimal missing data given the completeness of ICES administrative databases. Any missing data will be included as an additional missing data covariate.

Methods for additional analyses (e.g., subgroup analyses) {27d}

Pre-planned stratified analyses will include physician gender, career stage, patient volume (quartiles;Q1–Q4, where Q1 represents the lowest quartile and Q4 the highest), baseline overall prescribing (Q1–Q4), baseline unnecessary prescribing (Q1–Q4), virtual care (Q1–Q4), primary practice setting (emergency room, primary care), rural versus urban location, and whether physicians have signed up for MyPractice reports. We will explore equity as a factor for variation stratifying analyses according to regional socioeconomic status (SES) using the neighbourhood income quintile of practice location. We will present both stratified descriptive tables and adjusted model estimates with corresponding 95% confidence intervals. Any additional analyses not pre-specified in this protocol will be clearly labeled as exploratory in the results and tables of the final publication.

Interim analyses {28b}

No interim analyses or stopping guidelines are planned.

Protocol and statistical analysis plan {5}

The full trial protocol and statistical analysis plan (SAP) has been made publicly available at https://www.isrctn.com/ (*ISRCTN90477957*). Participant-level data cannot be made publicly

available due to legal and data agreements with data providers. Researchers may reach out to ICES Data & Analytic Services through das@ices.on.ca for access, in accordance with ICES policies. Aggregate tables and analytic code (de-identified) will be made available on reasonable request after publication.

Ethical considerations

A&F are recognized quality improvement initiatives that can be implemented without informed consent (5). Ethics approval was obtained from PHO's Ethics Research Board; REB# 2024-017.02 (Additional file 10) and includes a waiver of informed consent. Since modifying the feedback metric poses no risk to individual physicians, and seeking formal consent would create a greater burden than the intervention itself, an opt-out consent model aligns with the TCPS 2 guidance for the ethical conduct of minimal-risk clinical research. Physicians have had a previous opportunity to opt out of antibiotic prescribing feedback in Ontario. These (n=70) physicians will be excluded. All physicians included will receive a debrief letter for 12 months (December 2026) that includes their updated antibiotic prescribing feedback data.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {3d}

The trial is coordinated by the CANBuild-AMR Ontario investigator team, which is responsible for day-to-day trial management and implementation. Public Health Ontario serves as the trial sponsor and provides organizational and ethical oversight (REB# 2024-017.02). ICES is responsible for data linkage, data management, and secure analytic environments. Given the pragmatic, low-risk design and use of routinely collected administrative data, no separate trial

steering committee or endpoint adjudication committee has been convened; oversight is provided by the investigator team in collaboration with the sponsor.

Data monitoring

No Data Monitoring Committee (DMC) was established for this trial because the intervention (a single mailed A&F letter) is minimal risk, involves no patient-level clinical procedures, and uses routinely collected administrative data for all outcomes.

Frequency and plans for auditing trial conduct {29}

No formal monitoring or auditing of trial conduct is planned. Given the minimal-risk nature of the intervention and the use of administrative data for all outcomes, ongoing safety monitoring by an independent Data Monitoring Committee (DMC) was deemed unnecessary. Therefore, ongoing safety monitoring by an independent DMC was deemed unnecessary.

Protocol amendments {31}

Any modifications to trial protocol (including any changes in letter format or delivery method) will be documented with a rationale submitted to the PHO Ethics Review Board and updated in the trial registry.

Consent or assent

This study uses routinely collected administrative data and mailed A&F letters. As described in the Ethical considerations section, A&F initiatives are recognized as minimal-risk quality improvement activities and may be conducted without written informed consent. Physicians previously had the option to opt out of receiving antibiotic feedback letters, and those who opted out (n=70) are excluded from this trial. Participating physicians may opt out of future letters using the link or QR code included in the mailed materials.

Dissemination policy {8}

The results of our findings will be shared publicly through conferences, peer-reviewed publications, and webinars to the public and the medical community through Public Health Agency of Canada and Choosing Wisely Canada. Local presentations to public health agencies and ministries of health will further provide avenues to share our findings and promote uptake of embedding antibiotic feedback into routine quality improvement practices across healthcare systems in Canada. Aggregated level data will be shared in publications and presentations. The de-identified results may be shared with other public health partners directly.

Trial status

Protocol version: 1.0 (17 December 2025)

Recruitment status: Recruitment has completed

Planned recruitment start date: December 2025

Estimated recruitment completion date: December 2025 (one-time mailed letter)

Estimated study completion: June 2026

Abbreviations

A&F: Audit and feedback

AMR: Antimicrobial resistance

APR: Antibiotic prescribing rate

CER: Comparative effectiveness research

CIHR: Canadian Institutes of Health Research

DMC: Data Monitoring Committee

ODB: Ontario Drug Benefit

OH: Ontario Health

PICO(T): Population, Intervention, Comparison, Outcome, Time

PHO: Public Health Ontario

RCT: Randomized controlled trial

RR: Rate ratio

SES: Socioeconomic status

TCPS 2: Tri-Council Policy Statement 2

UAP: Unnecessary antibiotic prescribing rate

Declarations

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Authors' contributions {3a}

Conceptualization: All authors

Methodology: All authors

Investigation: KLS, KR (data collection and analysis)

Writing – Original Draft: KR (main manuscript text)

Writing – Review & Editing: All authors

Funding Acquisition: All authors

Supervision: KLS

Project Administration: KR

Guarantor of the work: KLS

Funding {7a}

The funder CIHR, provided financial support but had no role in the study design; collection, management, analysis, or interpretation of data; writing of this protocol; or decision to submit the manuscript for publication. (CIHR Funding # 189918).

Availability of data and material {6}

The datasets supporting the conclusions of this study are held securely in coded, de-identified form at ICES. Legal data sharing agreements between ICES and data providers (e.g., healthcare organizations and government) prohibit ICES from making the dataset publicly available. Access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca).

The full dataset creation plan and underlying analytic code are available from the authors upon request, with the understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and may require modification before use or may be inaccessible.

Access will be provided for non-commercial research purposes only, in compliance with all applicable privacy and legal requirements.

Ethics approval and consent to participate {30}

This study involves human participants and was conducted in accordance with the principles of the Declaration of Helsinki. Ethics approval was obtained from the PHO Research Ethics Board; REB# 2024-017.02 (Additional file 10). If you would like to speak to someone regarding the ethical approval of this project, please contact the PHO Research Ethics Coordinator at ethics@oahpp.ca.

Consent for publication

This manuscript does not contain any individual person's data in any form (including individual details,). Therefore, consent for publication is not applicable. All authors reviewed and approved the final manuscript.

Competing interests {7b}

The authors declare the following competing interests:

Alexander Singer reports all support for the present manuscript from CIHR - Peer reviewed research grant; support for attending meetings and/or travel from Health Science Centre Foundation (Winnipeg), Children's Hospital Foundation (Winnipeg), Canadian Allergy, Asthma and Immunology Foundation, Skin Investigation Network of Canada, Pfizer Inc. (Improving Health Equity in IBD through Disparities Research Fund) - Peer reviewed research grants; and consulting for BMX consulting.

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Fizza Gilani reports on employment with the College of Physicians & Surgeons of Alberta.

Jonathan Lams reports employment with Canada's Drug Agency.

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Terry Wuerz reports payment for expert testimony from Field Law, Edmonton, Alberta, and Carbert Waite LLP, Calgary, Alberta, for firms representing Alberta Health Services.

All other authors declare that they have no competing interests.

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