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Harmonising definitions of multiple long term conditions for inflammation research: a co-production approach

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Abstract

Objective Inflammation is implicated in many chronic diseases, but its role in driving multiple long-term conditions (MLTCs) remains unclear. The InFLAIM programme aims to explore this potential link. Existing MLTC codelists are valuable but have not been designed for inflammation-focused research and often lack harmonisation across coding systems. This work aimed to develop a transparent, co-produced MLTC framework with harmonised codelists for epidemiological research, focusing on inflammatory conditions within the InFLAIM programme.

Results Using a systematic, co-produced approach, we combined literature review, clinical consensus, and patient input. From 8 sources, 363 candidate conditions were identified, refined to 60 validated MLTCs. Patients informed terminology and diagnostic experiences. Codelists were drawn from CALIBER (43), HDR UK Phenotype Library (4), MULTIPLY (8), with 7 developed de novo. Harmonisation covered Read v2, SNOMED CT, and Medcodeids. Quality assurance excluded 16.5% of codes and resolved 92 overlaps. We produced harmonised codelists for 60 MLTCs, comprising 7,426 validated MedCodeids. Clinical consensus identified 17 conditions with significant inflammatory components. Additional lists were developed for autoimmune and infectious diseases to support inflammation-focused analyses. This framework extends existing resources to meet the needs of inflammation-focused research, offering a transparent, harmonised, and patient-informed foundation for the InFLAIM programme.

Keywords Multiple long-term conditions, Multimorbidity, Co-production, Patient and public involvement, Medical coding, Electronic health records, Inflammation

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Introduction

The UK’s ageing population is living longer with complex health needs: two-thirds of adults aged 65 or older have at least two long-term conditions (MLTCs) [1–4], compared with one-third globally [1]. Policy efforts, including NICE (National Institute for Health and Care Excellence) guidelines [5] and NIHR’s (National Institute for Health and Care Research) strategic focus on MLTCs [6], are limited by the lack of standardised definitions. Existing frameworks vary in condition selection, coding, and disease groupings [7–9], limiting comparability across studies.

The InflAIM programme examines whether inflammation drives MLTC development, especially in socio-economically disadvantaged groups. Large-scale EHR data are crucial but pose methodological challenges: most MLTC codelists do not separate inflammatory from non-inflammatory conditions—e.g., Osteoarthritis and Rheumatoid Arthritis (RA) are often combined—reducing their value for inflammation-focused research. Differences in coding systems hinder harmonisation, and few frameworks incorporate lived experience, despite evidence that patients describe symptoms differently from clinical labels [2, 3]. Examining this with large-scale electronic health record (EHR) data is important but methodologically challenging.

To address these challenges, we developed a co-produced MLTC framework with three key innovations:

1. A targeted focus on identifying and prioritising inflammatory conditions within MLTC definitions;
2. The development of harmonised codelists across three major UK primary care coding systems; and
3. A methodology that integrates patient experience with clinical and coding expertise.

Methods

We employed a two-part methodology: (1) co-produced condition selection using an iterative, consensus-based process, and (2) the development of harmonised, interoperable codelists across UK EHR systems.

Condition selection

Stage 1: literature review

We conducted a pragmatic literature review to identify key sources informing disease inclusion criteria for defining MLTCs. Starting with the seminal paper by Barnett et al. [2], we conducted forward citation searching, supplemented by keyword searches across PubMed, Google Scholar, Scopus, and Web of Science. An overview of outcomes of the search strategy is shown in Fig. 1.

This process identified eight key sources: Barnett et al. [2], Ho et al. [3] MacRae et al. [4], GEMINI study [5], Dodds et al. [6], Lyall et al. [7], Head et al. [8], and Beaney et al. [9]. We systematically compiled all conditions identified across these sources. Conditions appearing in at least two of the eight sources comprised our provisional list of 363 conditions.

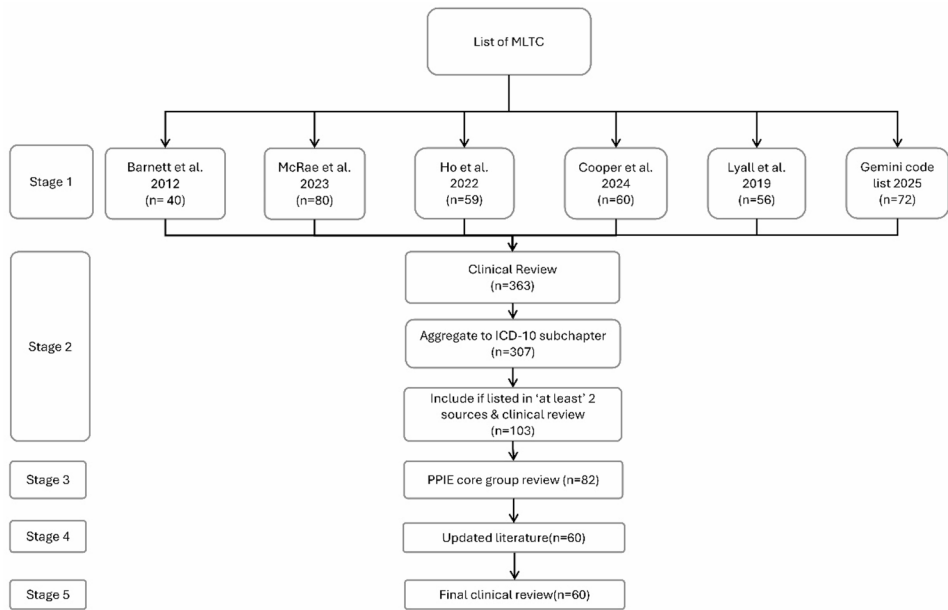


Fig. 1 Flowchart of inclusion/exclusion*. Flow diagram showing the process of identifying and refining multiple long-term conditions (MLTCs). Candidate conditions were sourced from Barnett et al. [2], McRae et al. [4], Ho et al. [3], Cooper et al. [10], Lyall et al. [7], and the GEMINI codelist (2023). Following clinical review (n = 363), conditions were aggregated to ICD-10 subchapter level (n = 307), filtered for inclusion if listed in ≥ 2 sources and validated through clinical review (n = 103), reviewed by the PPIE core group (n = 62), and subjected to final coding refinements. This process provided a final list of 60 MLTCs. (n) = number of long-term conditions reported

Stage 2: clinical expert review

A panel of three clinical experts—representing primary and secondary care, public health and psychiatry—reviewed the candidate conditions over several rounds, resolving disagreements by consensus. The final resulting refined list of MLTCs were categorised as chronic physical, mental, or infectious diseases.

Defining “chronic” was a key issue: published definitions range from disease durations of greater than 3 to 12 months [9, 11]. Rather than applying a strict threshold, the panel used clinical judgement instead of a strict cut-off. Conditions were excluded if they were acute, hereditary, congenital, childhood or pregnancy related. Long COVID was also excluded because it is coded as a broad, multi-system entity that cannot be positioned within a single-condition framework.

Stage 3: patient and public involvement (PPIE)

Our PPIE group comprised 5–7 individuals with lived experience of two long terms conditions or of caring for someone with them. Members’ conditions included rheumatoid arthritis (RA), depression and diabetes among others. Participants were all aged over 40 with 55% female and 45% male. The group including people from different ethnic, socioeconomic and seldom-heard communities.

Participants attended three separate group sessions involving whiteboard discussions on MLTCs, reviewing the clinical condition list and mind-mapping to integrate lived and clinical perspectives. These activities revealed differences in language and symptom framing, ensuring the findings reflected both patient experience and clinical understanding.

Stages 4 and 5: updated literature and final clinical review

Following the initial review stages, we re-examined the literature and coding sources to ensure completeness and identify any overlooked conditions, incorporating findings from the PPIE process. The clinical panel then undertook a final review to refine the list, resolve outstanding disagreements and reach consensus. The provisional conditions were then aggregated to ICD-10 subchapter level to align with established epidemiological groupings and ensure consistency across coding systems (Read v2, SNOMED CT, ICD-10).

Codelist development

Harmonised codelist development

Following condition selection, we developed comprehensive phenotyping algorithms for the condition set across three coding systems relevant to UK primary care research: Systematized Nomenclature of Medicine – Clinical Terms (SNOMED CT, UK Clinical Extension & International Edition), Read Code Version 2, and CPRD

(Clinical Practice Research Datalink) Aurum Medcodeids which were mapped to the relevant ICD-10 subchapters. These systems reflect the range of EHRs and research datasets included in the InFLAIM programme.

Hierarchical algorithm development

We used a hierarchical approach to develop phenotyping algorithms, prioritising sources with strong methodological rigor, validation and research use. This ensured consistent quality and semantic interoperability. Our primary source was the CALIBER (Cardiovascular disease research using LInked Bespoke studies and Electronic health Records) algorithms [12], chosen for their validated definitions and reproducibility across multiple studies. As CALIBER was developed using the CPRD GOLD database, we adapted codelists for CPRD Aurum using the mapping approach from Head et al. [8]. Secondary sources included the HDR UK Phenotype Library, recognised for expert clinical validation, and the MULTIPLY (MULTI-national consortia to study Polygenic risk scores by Large-scale health sYstems Initiative), which provides consensus-based phenotypes with transparent methods and primary care relevance [12].

Semi-automated development process

For conditions lacking published definitions, we implemented a systematic semi-automated development process. This began with ICD-10 concept expansion using the WHO API (World Health Organization, Application Programming Interface) (2019), followed by cross-mapping using NHS TRUD (Technology Reference data Update Distribution) files and the CPRD Aurum Medical Dictionary. Prioritising sensitivity in the initial stage, we applied automated filtering across five sequential categories: procedure-related, administrative and non-diagnostic, acute event, congenital/hereditary, and finally “not otherwise specified” or “unspecified” code exclusions. Where a code appeared across multiple condition lists, we used clinical adjudication to assign it appropriately.

Supplementary codelist development

Supplementary analyses followed two steps. First, the clinical panel identified a subset of the primary condition list with significant inflammatory pathophysiology. Second, for autoimmune and infectious diseases, we systematically sourced published codelists (e.g. Lyall et al. [7], Watson et al. [13], Janbek et al. [14]), harmonised across coding systems using the CPRD Aurum Medical Dictionary and the same methods as for primary codelists. Final lists were clinically curated and de-duplicated to exclude overlaps with the primary MLTC set.

Results

Condition selection outcome

The literature review identified 363 candidate conditions across eight key sources. Through a five-stage co-production process—including clinical expert review, patient and public involvement, and final adjudication. This was reduced to 60 conditions (Table 1; Fig. 2), each agreed by unanimous clinical consensus as relevant to MLTCs for the InflammAID programme.

A major methodological step was aggregating conditions to ICD-10 subchapters: 307 of the 363 were consolidated into broader groupings to enable harmonised cross-mapping, though this reduced granularity. After clinical and PPIE review of 103 subchapter-level groupings, the final set of 60 long-term conditions was selected. Conditions were classed as inflammatory when they involved active immune-driven tissue inflammation; grouped conditions were labelled inflammatory when key subtypes met this criterion. Autoimmune and infectious diseases were handled separately.

Insights from the PPIE group informed several aspects of condition selection. Members highlighted differences between clinical diagnoses and lived experience—especially for mental health and fluctuating conditions—prompting closer scrutiny of coding. Members described gout as chronic but episodic, and inflammatory bowel disease (IBD) as marked by debilitating flares, emphasising that such fluctuations often go uncaptured in clinical records. This input supported retention of conditions that may be inconsistently coded but consistently described as impactful. Participants further stressed that conditions such as, RA, Multiple Sclerosis and systemic lupus erythematosus affect multiple organ systems, prompting scrutiny of how conditions were grouped for analysis.

The final list included conditions from a wide range of clinical domains: cardiovascular, metabolic, endocrine, musculoskeletal, respiratory, neurological, mental health, gastrointestinal, renal, dermatological, haematological, oncological, and infectious diseases.

Of the final MLTC list, 17 conditions were identified by clinical consensus as having significant inflammatory pathophysiology, including RA, inflammatory bowel disease and asthma (see Table 1, inflammatory conditions indicated by *).

To further support InflammAID's focus on inflammation, we identified a comprehensive list of autoimmune and infectious disease conditions through separate literature and clinical reviews for targeted phenotyping.

Codelist development

Phenotyping algorithms were successfully developed for all 60 conditions using a hierarchical approach to

sourcing, based on methodological rigour, validation status, and research adoption.

- CALIBER provided codelists for 43 conditions (71.6%), forming the majority of the final set.
- HDR UK Phenotype Library contributed 4 (6.6%), including ischaemic heart disease and tuberculosis.
- MULTIPLY Initiative provided 8 (13.3%), including systemic connective tissue disorders.
- Codelists for seven conditions (11.6%) were developed de novo through a semi-automated process, for conditions such as hypoparathyroidism and in situ neoplasms.
- Of the conditions sourced above, two (3.2%) required hybrid approaches combining multiple sources.

The initial compilation included 8,898 Medcodeids across three UK coding systems. Following automated and manual filtering to improve diagnostic precision, 1,472 codes (16.5%) were excluded, resulting in 7,426 validated codes. These were harmonised across SNOMED CT, Read Version 2, and CPRD Aurum Medcodeids (Fig. 2).

Automated quality checks flagged 92 SNOMED CT concepts and 160 Read/Medcodeids that mapped to multiple conditions. These were adjudicated by clinical experts, with codes either reassigned to a single most appropriate condition or retained across multiple lists where justified by clinical overlap (Additional file, Table 1). The taxonomic structure of the clinical codelists for 60 LTCs is visualised as a radial dendrogram in the Additional file, Fig. 1.

Supplementary codelists were developed for 228 autoimmune and 2,107 infectious diseases, based on a systematic sourcing and harmonisation process. The autoimmune codelist included 489 Read codes and 341 SNOMED CT codes. The infectious disease list comprised 2,107 Read codes and 1,390 SNOMED CT codes (see Additional files, Tables 2 and 3).

Discussion

This study presents a systematically developed MLTC framework, tailored to support inflammation-focused research. Through a five-stage co-production process, we integrated evidence from the literature, clinical consensus, and public involvement to define a robust condition set and harmonised codelists. This addresses limitations in prior frameworks, which often lack transparency, patient input, or interchangeability across coding systems.

Our approach was shaped by the aims of the InflammAID programme, exploring inflammatory mechanisms in multimorbidity. This influenced condition selection—prioritising those with inflammatory pathophysiology—and the decision to develop supplementary autoimmune and

Table 1 MLTC conditions, ICD-10 chapter and inflammatory indicator

ICD-10	MLTC condition
A15-A19	Tuberculosis*
A69	Other spirochaetal infections*
B18-B19	Chronic viral hepatitis*
B20-B24	HIV disease
C00-C80, C97, D37-D44, D47, D48	Malignant neoplasms
C81-C96	Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue
D00-D09	In situ neoplasms
D50	Iron deficiency anaemia
E00-E07	Disorders of thyroid gland
E10-E14	Diabetes
E20	Hypoparathyroidism
E21	Hyperparathyroidism
E27	Addison's disease
F00-F03	Dementia
F10-F19	Drug or alcohol misuse
F20-F29	Schizophrenia
F30-F39	Mood disorders
F40-F48	Neurotic, stress-related and somatoform disorders
F50	Eating disorders
G20-G21	Parkinson disease
G35, H46	Multiple sclerosis (and optic neuritis)*
G40, F80.3	Epilepsy
G43	Migraine
G47	Sleep disorders
G61-G64	Polyneuropathies and other disorders of the peripheral nervous system
H25	Cataract
H33	Retinal detachments and breaks
H35	Other retinal disorders (Macular degeneration)
H40-H42	Glaucoma
H53-H54	Visual disturbances and blindness
H81.0	Meniere disease
H90-H91	Conductive and sensorineural hearing loss
I05-I09	Chronic rheumatic heart diseases*
I10-I15	Hypertensive diseases
I20-I25	Ischaemic heart diseases
I30-I52	Other forms of heart disease
I60-I69	Cerebrovascular Disease
I70-I79	Disease of arteries, arterioles and capillaries
I80-I89	Diseases of veins, lymphatic vessels and lymph nodes, note elsewhere classified
J30-J32	Rhinitis and Sinusitis*
J40-J47	Chronic lower respiratory diseases*
J84	Other interstitial pulmonary diseases*
K21, K27, K29	Diseases of oesophagus, stomach and duodenum
K50-K52	Noninfective enteritis and colitis*
K57	Diverticular disease of the intestine*
K58	Irritable Bowel Syndrome
K70-K77	Diseases of the liver
K80-K87	Disorders of gallbladder, biliary tract and pancreas
L20-L30	Dermatitis and eczema*
L40	Psoriasis*
M05-M14	Inflammatory polyarthropathies*
M15-M19	Arthrosis
M30-M36	Systemic connective tissue disorders*

Table 1 (continued)

ICD-10	MLTC condition
M45	Ankylosing spondylitis*
M47, M51	Spinal degenerative disease
M80-M85	Disorders of bone density and structure
N18-N19	Chronic kidney disease
N40-N42	Disorders of the prostate
N70-N77	Inflammatory diseases of the female pelvic organs*
N80	Endometriosis*

*Inflammatory condition

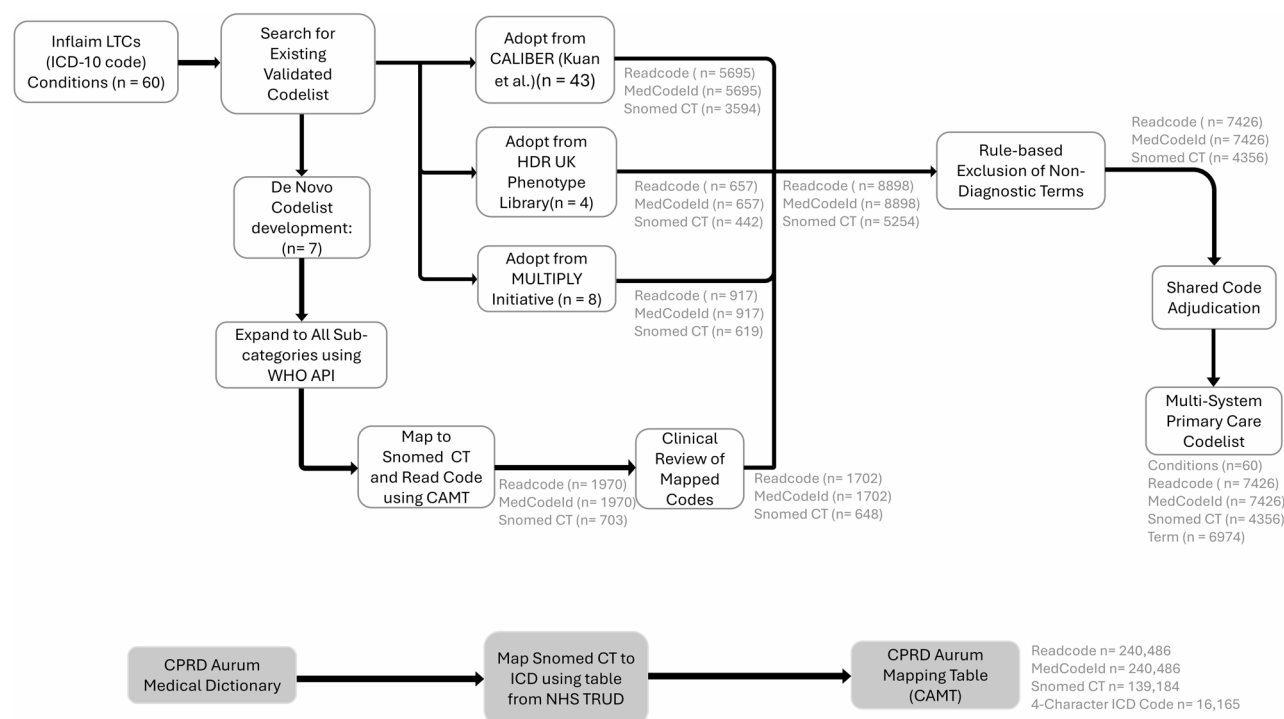


Fig. 2 Workflow for the development and validation of 60 harmonised phenotyping algorithms. * Workflow for development and validation of harmonised phenotyping algorithms. The diagram illustrates the hierarchical sourcing strategy, integration of published and de novo algorithms, and the multi-stage filtering and adjudication processes that produced the final validated codelists across three UK primary care coding systems. Counts shown in each block indicate the number of unique codes (concepts/terms) present at that stage within the respective coding system

infectious disease codelists. Choices around granularity were guided by biological relevance; for example, grouping spinal degenerative conditions while treating inflammatory arthropathies as distinct.

Patient and public contributors played a central role, prompting closer scrutiny of mental health and fluctuating conditions and highlighting mismatches between clinical codes and lived experience. This strengthened the framework's alignment with both diagnostic logic and real-world complexity.

Codelists were developed using a hierarchical strategy, prioritising validated algorithms across three UK coding systems. Where definitions were absent, we derived new algorithms using a semi-automated pipeline with clinical adjudication and automated checks to improve specificity and resolve overlaps. ICD-10 alignment and mapping

tables enable consistent and reproducible use across datasets such as CPRD, UK Biobank, ELSA (English Longitudinal Study of Ageing) and international resources (e.g. Global Burden of Disease, WHO Global Health Observatory, OECD, Organisation for Economic Co-operation and Development). Future work will include validating use of the framework by linking it to key epidemiological outcomes including morbidity, mortality and age-specific disease burden.

Limitations

Our literature review focused on key sources, not exhaustive coverage. Clinical review involved judgement calls on chronicity and condition grouping. Aggregation of conditions to ICD-10 sub-chapter level will inevitably have resulted in some loss of granularity for certain

conditions. Despite rigorous harmonisation, some coding inconsistencies may persist. The PPIE process was qualitative and influential, but its specific impact is not easily measured.

Overall, this work delivers a flexible, transparent and interoperable MLTC identification framework with broad applicability. By explicitly incorporating inflammation as a core mechanism and combining clinical evidence with patient perspectives, it enhances the validity and relevance of MLTC research.

Abbreviations

RA	Rheumatoid arthritis
MLTC	Multiple long-term conditions
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
EHR	Electronic Health Records
PPIE	Patient and Public Involvement and Engagement
CPRD	Clinical Practice Research Datalink
IBD	Inflammatory bowel disease
ICD-10	International Classification of Diseases, 10th Revision
SNOMED CT	Systematized Nomenclature of Medicine Clinical Terms
CALIBER	Cardiovascular disease research using linked bespoke studies and electronic health records
AI MULTIPLY Initiative	AI for Multiple Long-Term Conditions and Polypharmacy across diverse UK populations and inform health care pathways
TRUD	Technology Reference data Update Distribution
ELSA	English Longitudinal Study of Ageing
OECD	Organisation for Economic Co-operation and Development
HDR UK	Health Data Research UK
WHO	World Health Organisation
NHS	National Health Service
API	Application Programming Interface

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13104-025-07626-0>.

Supplementary material 1.
Supplementary material 2.
Supplementary material 3.
Supplementary material 4.

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Author contributions

DA: Conceptualisation, Methodology, Data curation, Formal analysis, Investigation, Writing original draft; CD: Conceptualisation, Methodology, Investigation, Patient and public involvement and engagement, Writing original draft; EK: Methodology, Formal analysis, Writing review & editing; TZ: Methodology, Formal analysis, Writing review & editing; MHA: Methodology, Formal analysis, Writing review & editing; CF: Methodology, Validation, Writing review & editing; BAHJ: Methodology, Writing review & editing; JG: Methodology, Patient and public involvement and engagement, Writing review & editing; JAF: Methodology, Validation, Writing review & editing;

AJM: Conceptualisation, Methodology, Validation, Writing review & editing. All authors contributed to the interpretation of the findings, critically revised the manuscript, and read and approved the final manuscript.

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Data availability

The complete validated codelist repository are available at <https://github.com/Inflaim-Study>. All codelists are provided in multiple formats compatible with major UK electronic health record systems.

Declarations

Ethics approval and consent to participate

All methods were carried out in accordance with the principles outlined in the Declaration of Helsinki. PPIE involvement and engagement in the Inflamm programme was approved by the University of Chester, Faculty of Health, Medicine and Society, School of Nursing and Midwifery's Research Ethics Sub-Committee in May 2025. (REC Reference: FRC0425-954). PPIE Participants were informed about the aims and process of the programme at recruitment, provided with a programme handbook, and advised that they could withdraw from the programme at any time. Participants also provided informed written or verbal consent for the outcomes of the meetings to be shared for academic dissemination and other relevant purposes.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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