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Patient and Public Involvement in Pharmacoepidemiological Research: An Environmental Scan of an Emerging Area

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Keywords: methods | patient and public involvement | pharmacoepidemiology

ABSTRACT

Background: Patient and public involvement (PPI) in research is required to improve the relevance, feasibility, and interpretability. However, research on PPIs in pharmacoepidemiology (PE) is still limited. This study aimed to provide an overview of PPI implementation in pharmacoepidemiology through an environmental scan.

Methods: The environmental scan combined systematic reviews and expert interviews. A systematic review was conducted in MEDLINE, EMBASE, and the Cochrane Library from January 1, 2010, to June 30, 2023, to identify PE studies in which PPIs were mentioned. An additional review covered *British Medical Journal's* (BMJ) original articles from January 1, 2019, to June 30, 2023, via a similar method. In parallel, a cross-sectional study was conducted with a standardized questionnaire for French PE research teams, involving interviews via videoconference.

Results: We identified 3615 references for screening, among which 232 were selected for full-text screening. However, no studies have reported the use of PPIs in PE studies. The additional BMJ review identified 1058 references, 74 of which met the full-text selection criteria, and eight were included. Of 13 French PE research teams surveyed, three had prior PPI experience, and 12 affirmed the relevance of PPI in PE. The respondents identified barriers such as PE's complexity ($n=9$). They suggested training for patients ($n=9$) and collaboration with specialist teams ($n=5$) to facilitate PPI.

Conclusion: Our environmental scan highlighted the emergence and relevance of PPIs in PE studies, even though they are still uncommon. Tools are needed to acculture and assist PE researchers in engaging in PPIs.

1 | Introduction

The National Institute of Health and Care Research (NHIR) defined patient and public involvement (PPI) in research as research being carried out “with” or “by” members of the public rather than “to,” “about,” or “for” them [1]. PPI is acknowledged as a qualification for high-quality research and is highly

encouraged [2, 3]. PPI can improve the relevance of research subjects [4, 5], feasibility of projects [6], interpretation of results, and communication with civil society [6, 7] and can concern all phases and types of health research. Various methods of setting out PPIs have been described and can be classified into four levels [8]: (i) information, (ii) consultation, (iii) collaboration, and (iv) coproduction.

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Summary

- PPIs in pharmacoepidemiology are not noticeable, as this approach is rarely implemented or reported.
- French pharmacoepidemiology researchers consider patient and public involvement to be relevant in this discipline.
- Specific tools, inherent to the complexity of pharmacoepidemiology, are needed to deploy PPI approaches.
- The impact of a PPI approach in pharmacoepidemiology must be evaluated.

PPI in drug research is being developed as attested by international and national agencies promoting the inclusion of patients' perspectives. The European Medicines Agency (EMA) has promoted these approaches since 1995 and includes stakeholders (i.e., patients, the public, and professionals) on its scientific committees [9]. In 2001, the US Food and Drug Administration (FDA) established the Patient Representative Program, which allows stakeholders to provide advice based on their experiential knowledge [10]. In France, the French Medicines Agency (ANSM) involves users of expert advisory committees. These initiatives mainly concern the drug development phases, experimental drug research, and in the post-marketing phase, pharmacovigilance [9–15]. However, little is known about PPIs in pharmacoepidemiological studies. A 2019 systematic review highlighted that a few pharmacoepidemiological studies involved patients [16]; this might be related to the inherent methodological complexity and use of large databases in PE [17]. Since then, recommendations on PPI implementation in Data-Intensive Health Research have been published to encourage its development [18, 19].

The present study aimed to provide an overview of PPI implementation in pharmacoepidemiology through an environmental scan combining two methodologies. First, this was a systematic review, the aim of which was to describe the PPI process in pharmacoepidemiological research. Second, a cross-sectional survey aimed at describing the frequency and processes of PPI use in pharmacoepidemiological research was carried out by French academic pharmacoepidemiological research teams.

2 | Methods

2.1 | Systematic Review of the Literature

We performed a systematic review using the PRISMA statement to guide the reporting [20]. Our review was recorded on PROSPERO under the registration number CRD42023409929.

2.1.1 | Inclusion Criteria and Search Strategy

The included records were original articles published in English from January 1, 2010, to June 30, 2023, on PE studies¹ as defined by B.L. Strom et al. [21], integrating a PPI²

process [22]. Randomized controlled trials and review articles were excluded. References of relevant reviews were also screened. This systematic review involved searching PubMed/MEDLINE, EMBASE, Cochrane, and Wiley Online Library. The search strategy used main subject terms related to PE and PPI (Appendix S1, Table 1).

2.1.2 | Selection Process

The records underwent deduplication and selection using RAYYAN software [23]. Two reviewers (J.R. and Y.B.) independently conducted a double-blind, two-stage selection. In cases of disagreement, a third reviewer (A.H.) was involved. The first phase focused on titles/abstracts, and the second on full texts. The first phase's criteria targeted PE studies, not PPIs, to avoid excluding relevant articles.

Of the 3758 references identified (Appendix S2 Figure 1), none mentioned stakeholder involvement in PE studies as defined, resulting in no included studies. A new hypothesis was proposed: PPI might have occurred but was unreported or undetectable by keyword search. To identify articles involving stakeholders, even if not explicitly mentioned, we opted for a new research method. We focused on articles in the *British Medical Journal* (*BMJ*), which has mandated a "PPI" paragraph since January 1, 2019.

2.2 | Update of the Review: Focused *BMJ* Search

2.2.1 | Inclusion Criteria and Search Strategy

The same inclusion criteria were applied except for the date and database. The records included were published between January 1, 2019, and June 30, 2023, in the *BMJ*. Records meeting the selection criteria were searched in the PubMed/MEDLINE database. Only the main term "PE" of the systematic review search strategy was used (Figure 1 and Appendix S1, Table 1).

TABLE 1 | Justifications advanced by the authors for not involving stakeholders in their pharmacoepidemiological studies.

Justifications advanced by the authors	Number of studies concerned (<i>N</i> = 66)
No justification	31
PPI ^a perceived as not suitable due to methodological considerations (confidentiality of data, methodological difficulties)	19
Urgency of the study (COVID-19 context)	10
Lack of funding	6
Not part of the research team's objectives	1

^aPPI: Patient and public involvement.

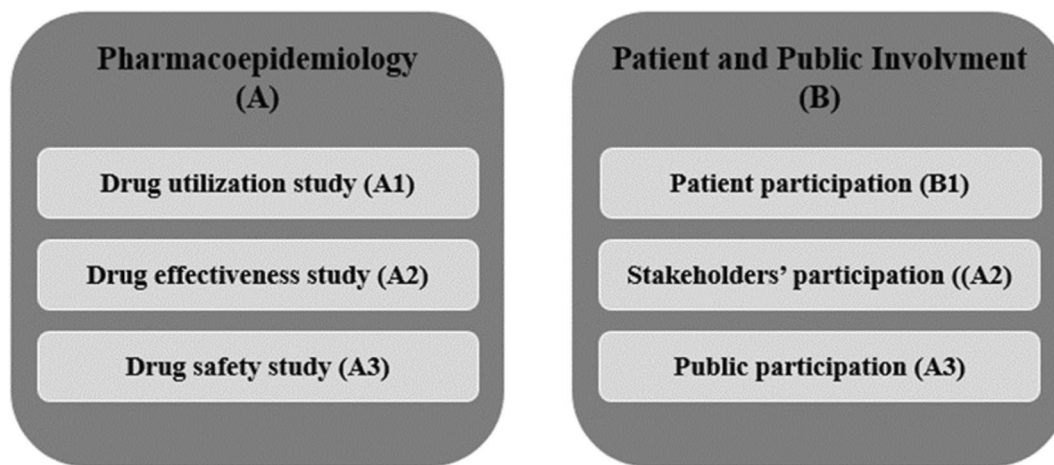


FIGURE 1 | Search strategy: (A1 or A2 or A3) and (B1 or B2 or B3).

2.2.2 | Selection Process

The first selection phase focused on titles/abstracts and aimed at identifying PE studies. The second selection phase was carried out in the “Patient and Public Involvement” paragraph to identify records with PPIs. The files that reported a PPI process in the dedicated paragraph were then read in full text for data extraction. For records excluded because they did not involve stakeholders, we have described the reasons given by the authors in the dedicated paragraph.

2.2.3 | Data Extraction and Quality Appraisal

The following data were extracted from the records: bibliometric information, study characteristics (aim; application fields of PE, i.e., drug utilization, drug effectiveness, or drug safety; study design; and data sources), and the involvement process (aim of PPI; PPI methods; number of patients involved; PPI results; discussion, perspectives on PPI process; and level of PPI). Quality assessment of the PPI report was carried out independently by two reviewers using the short version GRIPP2 [24]. The GRIPP2 checklist is a guidance for reporting PPI in health and social care research. It is composed of five items on aims of PPI, methods used to involve patients and publics, results and benefits of the PPI approach, discussion on the PPI contribution, and critical perspective. Based on the reading of the whole paper, each item was rated according to a color: (i) green: presence of the item clearly stated; (ii) orange: presence of the item but not precisely described; and (iii) red: absence of the item. A narrative synthesis summarizing the PE methodologies, the PPI processes, and the PPI quality assessment was conducted.

2.3 | Cross-Sectional Survey

2.3.1 | Population and Study Design

A cross-sectional observational study was conducted in the form of a questionnaire. The study included PE research teams in France who agreed to participate. We proposed the participation

of all French academic research teams identified (selection process detailed in Appendix S3 Document 2).

2.3.2 | Survey Construction

A semistructured questionnaire was developed, including 24 questions in three parts: (i) experiences of PPI in French PE studies; (ii) Respondents’ opinions on the PPI in PE and its feasibility; and (iii) barriers, levers, and tools needed for PPI implementation (Appendix S3 Document 1). This questionnaire was based on the methodology described in the INVOLVE “Briefing notes for researchers” recommendations [22]. The questionnaire was proofread by a patient-partner involved with our research team and the scientific coordinator of Epi-Phare.

2.3.3 | Data Collection

An initial email invitation was sent to each team’s scientific leader. If there was no response, the invitation was reiterated four times. Participating researchers were then interviewed via videoconference by a trained interviewer using the questionnaire. Responses were pseudonymized and transcribed into an Excel file. The questionnaire included yes/no, multiple-choice, and open questions for comments and additional remarks.

2.3.4 | Data Analysis

Responses to closed and multiple-choice questions were described as categorical variables using frequency. The free text answers were analyzed verbatim in three stages: (i) harmonization of the terms used (e.g., *DPI* = declaration of links of interest); (ii) classification of quotes into themes; and (iii) identification of the most relevant quotes to illustrate each theme. Themes were then attached to the relevant closed questions to illustrate the quantitative results. In the Results section, quotes are provided with the acknowledgment of the respondents who expressed them, indicated as R1 for respondent 1.

3 | Results

3.1 | Review of PE Articles Published in the *BMJ*

3.1.1 | Selection of Articles

The literature search yielded 996 records. After screening, 922 records that did not meet the PE study criteria were excluded. Of the 74 remaining articles, 66 did not meet the PPI inclusion criteria. Of the 66 excluded studies without stakeholder involvement, 31 lacked justification. The justifications in the remaining 35 articles were homogeneous (Table 1).

Thus, eight studies were selected for data extraction (Figure 2).

3.1.2 | Study Characteristics

Table 2 presents data from the included studies conducted in England ($n=6$), the United States ($n=1$), and Australia ($n=1$). The research phase concerned with PPI was described in 6 studies. Stakeholders were involved in the study design ($n=3$), protocol review ($n=2$), and proofreading of the results and the manuscript ($n=2$). Five studies mentioned the stakeholder profiles of those patients affected by the drug exposure studied. No information was provided on stakeholder recruitment, and the PPI process was briefly mentioned by the authors. Based on the reporting of authors, PPI helped redefine the research question

and criteria ($n=3$), clarify results ($n=2$), and create adapted tools ($n=2$). Two studies reflected critically on PPI benefits, either confirmation of the public's interest in research or a data collection tool in line with patients' priorities. Three levels of participation were identified: consultation ($n=2$), collaboration ($n=3$), and co-production ($n=3$).

3.1.3 | Quality Assessment

According to the short GRIPP2 [24], the reports of the involvement process within the included studies were of low quality³ (Figure 3). Indeed, 4 of 8 studies clearly stated the objective of PPIs, and only one described the recruitment method and the process used. Furthermore, two studies discussed the contribution of PPIs to their studies, but none mentioned their perspectives.

3.2 | Cross-Sectional Survey

3.2.1 | Sample Characteristics

Twenty-four French PE research teams were identified and contacted by email between June 23, 2023, and November 15, 2023. Of the 24 teams identified, 13 (54%) were ultimately interviewed. Six teams declined because they had never involved patients, and 5 requests went unanswered.

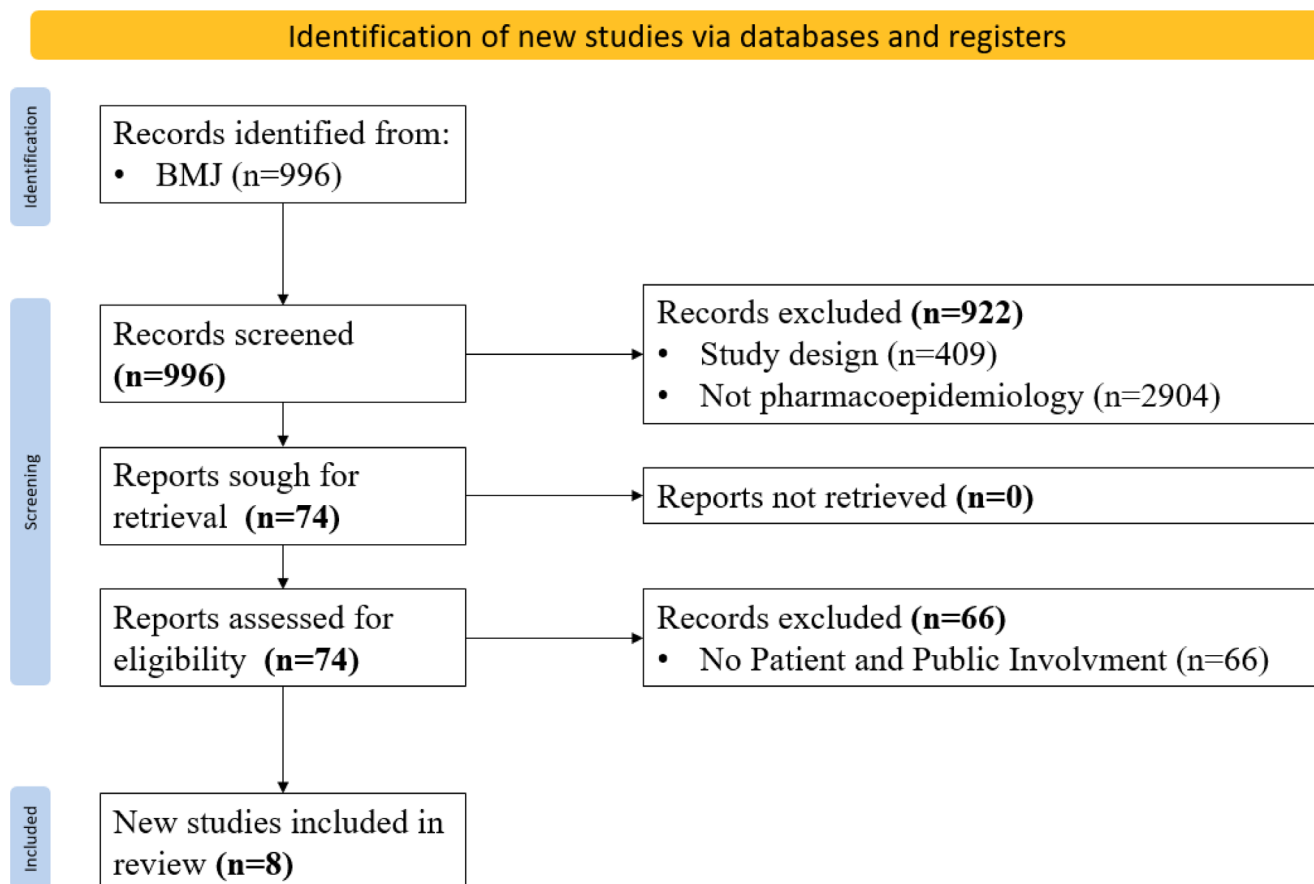


FIGURE 2 | PRISMA flowchart of the *BMJ* review.

TABLE 2 | Description of studies included in the *BMJ* review.

Author, year, country	Aim of the study	Application fields of PE ^a	Study design	Data sources	Aim of PPI ^b	PPI ^b methods	Number of patients involved	Results of PPI ^b	Discussion, perspectives on PPI ^b process	Level of participation
M Gharbi et al. 2019 [25] UK	To evaluate the association between antibiotic treatment for urinary tract infection and severe adverse outcomes in elderly patients in primary care	Drug safety	Retrospective population-based cohort study	Clinical practice research datalink (CPRD) linked to the office for national statistics	To review the protocol	Former elderly patients involved	Two	Research question refined protocol improved	No description	Collaboration
C G Mazariego et al. 2020 [26] Australia	To assess treatment-related changes in quality of life up to 15 years after diagnosis of localized prostate cancer compared to men randomly selected	Drug effectiveness	Prospective population-based cohort study	Patients were identified through the New South Wales Cancer Registry	To review the data collection questionnaire	Patients and members of the public (no selection criteria described)	No description	The questionnaire was amended to reflect patients and members of public perceptions	The questionnaire reflects patients' priority	Consultation
H Ahmed et al. 2021 [27] UK	To evaluate the association between untreated, community-acquired, respiratory tract infections and bleeding in oral anticoagulant users	Drug safety	Self-controlled case series study	CPRD GOLD	No description	Patients who used warfarin or direct oral anticoagulants recruited in the lead author's practice Formal patient representatives were recruited from health and care research wales and anticoagulation UK	Three	Helped shape the question and objectives, provided valuable support with interpretation of study findings	No description	Coproduction

(Continues)

TABLE 2 | (Continued)

Author, year, country	Aim of the study	Application fields of PE ^a	Study design	Data sources	Aim of PPI ^b	PPI ^b methods	Number of patients involved	Results of PPI ^b	Discussion, perspectives on PPI ^b process	Level of participation
J Hippisley-Cox et al. 2021 [28] UK	To derive and validate risk prediction algorithms to estimate the risk of COVID-19-related mortality and hospital admission in UK adults after one or two doses of COVID-19 vaccination	Drug effectiveness	Prospective population-based cohort study	QResearch database linked to the national immunization database of COVID-19 vaccinations	To frame the research question, identify predictors, and develop plans for design and implementation of the study	Patients (no selection criteria described)	No description	No description	No description	Coproduction
J Hippisley-Cox et al. 2021 [29] UK	To evaluate the association between COVID-19 vaccines and the risk of thrombocytopenia and thromboembolic events among UK adults	Drug safety	Self-controlled case series study	National immunization management system linked to the national data for mortality, hospital admissions, and SARS-CoV-2 infection QResearch database	No description	Patient and public involvement advisory panel of Oxford university's Nuffield department of primary care health sciences	No description	Identified priority questions Lay summary has been developed including an infographic	No description	Collaboration

(Continues)

TABLE 2 | (Continued)

Author, year, country	Aim of the study	Application fields of PE ^a	Study design	Data sources	Aim of PPI ^b	PPI ^b methods	Number of patients involved	Results of PPI ^b	Discussion, perspectives on PPI ^b process	Level of participation
D Sumilo et al. 2022 [30] UK	To investigate the impact on child health up to age 5 years of a policy to use antibiotic prophylaxis for cesarean section before incision	Drug safety	Observational controlled interrupted time series study	The health improvement network (THIN) and the CPRD GOLD	To refine the objectives and assessment criteria	Lay parent contributors included in the steering committee 2 sessions of focus group with mothers and mothers to be, to present the protocol Associations completed a questionnaire about the protocol	Two parents Two associations	Outcomes refined Coproduction of the lay summary and the dissemination plans	The PPI process has confirmed the public's interest in this topic	Coproduction
G Nakafero et al. 2023 [31] UK	To develop and validate a prognostic model to inform risk-stratified decisions on the frequency of monitoring blood tests during long-term methotrexate treatment	Drug utilization	Retrospective cohort study	CPRD GOLD and CPRD Aurum	To select and prioritize the research question	Patients and members of the public (no selection criteria described)	No description	Discussion on the choice of the study design	No description	Collaboration
Y Xie, T Choi and Z Al-Aly, 2023 [32] US	To evaluate whether treatment with molnupiravir during the first 5 days of SARS-CoV-2 infection is associated with reduced risk of postacute adverse health outcomes in population with at least one risk factor for progression to severe covid-19	Drug effectiveness	Retrospective cohort study	US Department of veterans affairs health care databases	To review the manuscript	Members of public (no selection criteria described)	No description	Feedbacks on manuscript	No description	Consultation

^aPE: Pharmacoepidemiology.

^bPPI: Patient and public involvement.

	M Gharbi et al., 2019 ²⁰	CG Mazzariego et al., 2020 ²¹	H Ahmed et al., 2021 ²²	J Hippiseley-Cox et al., 2021 ²³	J Hippiseley-Cox et al., 2021 ²⁴	D Sumilo et al., 2022 ²⁵	G Nakafero et al., 2023 ²⁶	Y Xie et al., 2023 ²⁷
Aim	Orange	Green	Red	Green	Red	Green	Orange	Green
Methods	Red	Orange	Orange	Red	Orange	Green	Red	Orange
Results	Orange	Orange	Green	Red	Green	Orange	Green	Orange
Discussion and conclusion	Red	Orange	Green	Red	Orange	Green	Orange	Orange
Reflections / critical perspectives	Red	Red	Red	Red	Red	Orange	Red	Red

FIGURE 3 | Quality assessment of the PPI reporting process of the included studies according to the short GRIPP2.

TABLE 3 | PPI processes of the 3 French pharmacoepidemiology teams declaring the use of PPIs.

	Team 1	Team 2	Team 3
Field of PE ^a	Utilization	Utilization	Safety
Aim of PPI ^b	To specify the judgment criteria	To specify the judgment criteria	To communicate results to society
Recruitment method and description of patients	1 patient recruited by personal network	3 patients recruited in hospital services	Association patients
Implementation method	Participation in the scientific committee	Workshops	Workshops
Barriers to patient involvement	Difficulty recruiting patients Potential distance from the initial research subject	Difficulty recruiting patients	Difficulty recruiting patients
Positive impacts observed	Better relevance of the search topic	Patients' point of view different from that of researchers, allowing certain biases to be avoided	Better interpretation and dissemination of results Better societal acceptability of this type of study
Mention of PPI ^b in the publication	No	No	Works not yet published

^aPE: Pharmacoepidemiology.

^bPPI: Patient and public involvement.

3.2.2 | Experiences With PPIs in French Pharmacoepidemiological Studies

Among the 13 of 24 survey respondents, 3 reported prior PPI commitment, but only in one study per team, with no collaboration with patients at the team organization level. Based on survey answers, the processes used by these 3 teams are described in (Table 3).

3.2.3 | Respondents' Opinions on the Possibility of Implementing PPIs in PE

The survey responses are available in Table 4. One respondent did not consider the PPI process relevant because of the issues with which his pharmacoepidemiology studies on patients reported within the pharmacovigilance system. However, 12 out of 13 respondents stated that PPI was relevant in PE, although they mitigated their statement according to the phase of the

research concerned. The choice of the research topic could be guided by PPI to ensure to address patient and public priorities ($n = 8$).

R1 “The questions raised by patients about their treatments or care pathways could enable us to develop more relevant research topics”.

R9 “Patients are more expert than we are on their care pathways and can provide clarification or suggest an objective important to them”.

Regarding research protocol elaboration, some respondents felt that patients could be involved in specifying the research objectives ($n = 4/6$) and the judgment criteria ($n = 5/6$).

R8 “Chronically ill patients have expertise on certain points we do not have”.

TABLE 4 | Answers to the shared part of the survey.

Question	Responses (N=13)	Response = yes
Q-S-18: In which phase(s) do you think it would be relevant to include patients in your research project?	Choice of research topic	n = 8
	Elaboration of research protocol/parts of research protocol	n = 6
	Analysis and/or interpretation of results	n = 12
	Communication about the research project	n = 12
	Other	n = 0
Q-S-18B: In the elaboration of the protocol, they could be involved in:	Precision of research objectives	n = 4
	Precision of judgment criteria	n = 5
	Precision of the studied population	n = 0
	Other	n = 0
Q-S-18D: In communication about research projects, they could be involved in:	Communication to the general public	n = 12
	Scientific communication	n = 0
	Other	n = 0
Q-S-19: According to you, what positive outcomes could result from involving patients in your research projects?	Better relevance of research topics, addressing important questions for patients and professionals	n = 11
	Better feasibility of projects by reducing measurement biases (better definition of the population, objectives, or judgment criteria)	n = 2
	Better interpretation of results	n = 5
	Better dissemination of results and potential impacts on practices or the use of health products	n = 11
	Other	n = 0
Q-S-20: According to you, what negative outcomes could result from involving patients in your research projects?	Study slowdown	n = 4
	Departure from the initial research topic	n = 2
	Additional cost	n = 1
	Project failure	n = 0
Q-S-21: Which levers do you identify for involving patients in your research projects?	Other	n = 0
	Members of my research team are engaged in this process and are driving factors	n = 0
	It is a demand from funders or sponsoring agencies	n = 5
	The literature on the subject guides me in this process	n = 0
	It is a demand from patients or healthcare professionals	n = 2
Q-S-22: Which barriers do you identify for involving patients in your research projects?	Other	n = 0
	Lack of knowledge of the involvement process	n = 4
	Lack of a PPI champion	n = 0
	Lack of resources (recommendations, guides) available to support this process	n = 5
	Lack of time	n = 2
	Complexity of methodologies of this type of research for noninitiated individuals	n = 9
	Additional funding	n = 1
	Apprehension about discussing certain practice or care issues with patients	n = 3
	Difficulty in identifying and recruiting patients	n = 8
	Other	n = 0

(Continues)

TABLE 4 | (Continued)

Question	Responses (N=13)	Response = yes
Q-S-23: In what form could you imagine participation in your research projects?	Questionnaire	n=2
	Steering committee	n=4
	Workshops or working groups	n=8
	Individual interviews	n=0
	Focus groups (discussion)	n=1
	Other	n=0
Q-S-24: What tools might you need to engage or strengthen patient involvement in your research projects?	Standard framing documents	n=1
	Training for patients	n=9
	Training for researchers	n=6
	Roadmaps to build the engagement initiative	n=5
	Dedicated funding	n=4
	A PPI champion	n=0
	Other	n=0
Q-S-24-BC: What training would be useful to you?	Research training for patients	n=9
	Training in participatory qualitative methods	n=3
	Scientific popularization training	n=3
	Other	n=0
Q-S-24-D: What roadmaps would be useful to you?	A guide to assist in drafting the engagement protocol	n=4
	A model information sheet	n=0
	A model email template to send to patients	n=0
	Other	n=2

Other respondents ($n=7$) stressed that the complexity of PEs made it impossible to carry out PPIs during protocol elaboration. Twelve of the 13 respondents stated that they found it relevant to involve patients in the analysis and interpretation of results, but only 5 expected an impact on the interpretation. Finally, the relevance of PPI in disseminating results to civil society was recognized ($n=11$).

The most suitable form of PPI was workshops ($n=8/13$), followed by the integration of patients into the scientific committee ($n=4/13$).

The better relevance of research topics and better dissemination of results to civil society were the two main benefits expected by respondents ($n=11$ both), with some nuances depending on the type and subject of the study.

R8 “If the study is not about chronic diseases, I doubt the relevance of patient involvement.”

Respondents envisaged few negative consequences, the PPI approach was cited as a possible cause of the study’s slowdown ($n=4$).

R9 “As pharmacoepidemiologists, we are not used to working with patients and popularizing our work.”

3.2.4 | Barriers, Levers, and Tools for PPI Implementation

Several barriers, as shown in Figure 4, were validated among those proposed. The methodological complexity of PE studies ($n=9$) and recruitment of patients ($n=8$) were the biggest barriers.

R11 “In pharmacoepidemiology, knowledge of epidemiology as well as knowledge of drugs are needed.”

R6 “We need to find real user representatives i.e. the people who are most representative of our study population.”

R12 “The patients included must be representative of the population studied, but are the expert patients?”

Five respondents did not select any of the suggested levers and did not suggest any other. For other, one of the levers could be a request from the funding agencies ($n=5$).

In addition, some respondents would also be interested in a guide to help them implement a PPI approach and feedbacks from a team that has already conducted this approach in PE studies ($n=5$).

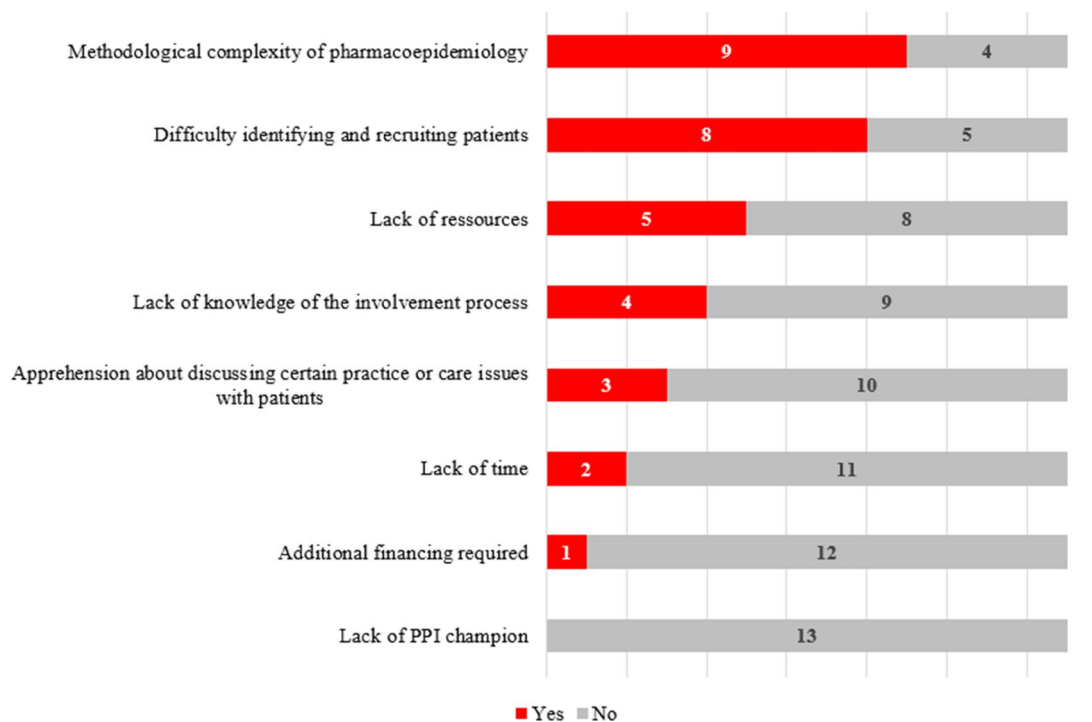


FIGURE 4 | Barriers to PPI in PE studies, according to respondents.

R9 “Popularizing our discipline is not easy, training with a few tools could be useful.”

R4 “A procedure drawn up by a team used to this type of initiative could make it easier for other teams to get to grips with it.”

4 | Discussion

Our study revealed that patient involvement in PE research is still limited. Indeed, our primary systematic review did not identify any PE articles that sufficiently reported PPI to highlight it using a traditional keyword search strategy. Additionally, a search of *BMJ* and PE articles in the PPI section confirmed that only a small proportion of PE studies published between 2019 and 2023 involved stakeholders. When that involvement occurred, the reporting did not comply with GRIPP2 standards. Furthermore, French PE researchers are interested in this approach, though it is not seen as relevant for all research phases. Challenges remain, such as recruiting patients and complex PE methods, highlighting the need for developing tools and training.

Implementing the PPI approach in PE seems feasible, although this practice is not common. Within this discipline, the PPI is favored in drafting the study protocol to refine the objectives and outcomes and during the valorization of results. Of the studies in our literature review, only Šumilo et al. involved stakeholders in all research phases [8, 22]. Our findings suggest that the preferred method for PPI in PE research is direct PPI in the scientific committee or through workshops, differing from interventional health research [33] where focus groups and interviews are common. We hypothesize that most studies involving patients in existing reviews were qualitative or mixed-method.

In Domecq et al.’s [34] review, 103 of the 142 included studies were qualitative which relates to a low level of engagement (consultation). This suggests that while PPI is less common in PE research than in other health studies (health services research or clinical research), when it occurs, the level of involvement is higher than consultation through qualitative inquiry, reaching coproduction with patients in decision-making committees. The high level of PPI can also be found in PV routine practice through patient participation of patients in EMA or FDA regulatory boards [10, 35].

Several hypotheses might explain this high level of involvement. First, this may result from the lead of the studies by teams experienced in PPI who can be supported by an accultured environment. Second, these findings might be due to feasibility concerns related to the direct inclusion of patients in a supervisory position throughout the study due to differences in research activities. Indeed, the frequent stages at which patients are involved in intervention research (i.e., construction of research documents, recruitment of patients, communication with services) are not present in PE.

Despite the feasibility of involving stakeholders in PE, its relevance is weighed by French PE researchers according to the type of study. They find it most relevant in studies focusing on pathology or chronic drug exposure, as patients’ experiential knowledge can refine the research project from conception to implementation. However, safety studies are viewed as less appropriate for stakeholder involvement due to their specific subjects and timeframes, although some studies in our review did implement these approaches [25–27, 29–31].

Our survey identified two primary barriers, prompting reflection on potential solutions for implementing PPI approaches. First, the methodological complexity of PE could limit the use of

PPI approach, essentially in the phase of drafting the protocol, analyzing and interpreting the results. This obstacle, mentioned in several studies [18, 33, 34, 36] could be overcome by popularizing the research for the involved stakeholders. The second main obstacle reported was identifying and recruiting patients for the studies, which has also been identified in the literature [33, 34]. Recruitment through hospital care units or patient associations seems to be the preferred method. The development of patient-partner groups within research units could be a facilitating solution [34]. Furthermore, the issue of patient representativeness was highlighted by respondents. In France, the “patient-partner” terminology lacks a standardized definition, causing confusion about the patients’ motivations, skills, and representativeness. The “patient-expert” concept [37], prevalent in France, may conflict with representativeness, as it refers to personal and experiential expertise in the disease [38]. However, people who have taken a step back can contribute their perspectives without the need for statistical representativeness.

Our survey enabled us to identify the tools that would be useful to teams for supporting coproduction approaches: PE methodology training for patients, qualitative methodology training for PE researchers, and tools dedicated to the PPI approach specific to PE, written and disseminated by teams that have already conducted this process. Moreover, we identified a lack of reporting of the PPI process, contrary to recommendations [18, 24, 39]. The short GRIPP2 could be mentioned in specific pharmacoepidemiology reporting tools such as RECORD-PE [40] so that researchers can refer to it.

The present study has several limitations. First, identifying studies that had conducted PPI using the classic research equation approach proved complex due to the lack of dedicated keywords/MeSH terms, reporting and standardized methodology. In addition, our search equation was built around the two blocks “PE” and “PPI”, so a combination of the keywords had to be present in the title and abstract. The second review we conducted helped address this limitation since we only used the PE block, which explains they could not appear in our first systematic review. Although the choice to focus solely on the *BMJ* represents a lack of representativeness of the active file of published pharmacoepidemiology studies. However, this method combined with expert interviews, provided a better understanding of PPI issues in PE. One limitation of our environmental scan is the number of researchers interviewed in the survey. The chosen methodology was intended to interview team leaders who had an overall view of practices and studies on the team. However, the opinion of the person in charge did not necessarily reflect the views of all the team members, and it might have been interesting to interview the researchers more widely. Similarly, this study was restricted to France to diagnose this approach’s deployment and the teams’ needs to implement it but it would be interesting to implement it on a wider international scale. Indeed, some countries seem to be more advanced in the practice of stakeholder involvement, as this is part of the quality of research required by funders, for example. An international cooperation, as proposed in the former International Society of Pharmacoepidemiology (ISPE) dedicated committee, could be relevant to share methodologies [18, 36, 41, 42]. Nevertheless, the results shed light on the views of French PE researchers on the relevance of PPI and also highlighted the two main barriers in PE and the tools that could be

used to overcome them. Finally, the methodology provide an overview based on complementary data sources, and it is one of the first studies conducted on this subject and could serve for observing PPI implementation in pharmacoepidemiology.

4.1 | Recommendations

The objective of this study was to comprehensively assess stakeholder engagement in pharmacoepidemiology. Based on our research and findings, we propose the following recommendations to advance PPI methodologies within the field of PE.

First, PPI in pharmacoepidemiological research could be advanced through strategic knowledge dissemination and collaborative mechanisms, including: establishing interdisciplinary research networks for systematic experience sharing, developing dedicated information platforms and forums to facilitate methodological tool exchange, integrating specialized PPI sessions within scientific congresses, facilitating structured dialogues with patient associations, and fostering collaborative networks that actively engage patient partners in research development and implementation.

Second, PPI in pharmacoepidemiological research could be encouraged through policy levers, including the development of detailed national guidelines, the facilitation of the regulatory framework, the inclusion of PPI criteria in research funding tenders and project evaluations, and the provision of targeted logistical and/or financial support to facilitate meaningful stakeholder engagement.

Finally, the systematic documentation and critical evaluation of participatory approaches in pharmacoepidemiological research should be systematically encouraged, with the aim of fostering comprehensive reflection on the methodological, ethical, and scientific implications of PPI in pharmacoepidemiological studies.

5 | Conclusion

Our environmental review highlighted the emergence and prevalence of PPI approaches in PE studies. However, these approaches are underdeveloped and difficult to identify. Despite the methodological complexity of PE, French researchers consider PPI to be relevant in these approaches, and PE teams require support tailored to the specificities of PE and provided by experts in PPI. Acculturation of the reporting and evaluation of the implementation of a PPI approach would enable critical reflection on the contribution of PPIs to PE studies.

5.1 | Plain Language Summary

Patient and public involvement (PPI) in research is now recommended as it increases the relevance, feasibility, and interpretation of studies. In pharmacoepidemiology (PE), this approach appears to be very limited. The aim of this study was to provide an overview of the implementation of PPI in PE studies through two methods. Two literature reviews were conducted

to describe the PPIs methodology in PE studies, as well as the barriers and levers reported by the authors. In parallel, a survey was conducted with a standardized questionnaire for French PE research teams, involving interviews via videoconference. Following the two reviews, 4615 articles were screened and 8 pharmacoepidemiological studies were included because of PPIs process. Of 13 French PE research teams surveyed, three had prior PPI experience, and 12 affirmed the relevance of PPI in PE. The respondents identified barriers such as PE's complexity ($n=9$). They suggested training for patients ($n=9$) and collaboration with specialist teams ($n=5$) to facilitate PPI. Our study highlighted the emergence and relevance of PPIs in PE studies, even though they are still uncommon. Tools are needed to acculture and assist PE researchers in engaging in PPIs.

Author Contributions

The study was conceived by J.R., J.H. and M.V. J.H. and M.V. supervised the study. The ethical procedures were carried out by J.R. and A.T. Data were collected by J.R., Y.B. and A.H. J.R. conducted all analyses and wrote the first version of the manuscript. All authors reviewed, contributed to and approved the final manuscript.

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Ethics Statement

The cross-sectional study was conducted after approval (approval number 23-1057) from the INSERM Ethical Evaluation Committee (*Institut national de la santé et de la recherche médicale, INSERM*). This study complied with general protection data regulation and the French regulation while conforming to the reference methodology MR-004 (number 23-075 in the general treatment register of Hospices Civils de Lyon).

Consent

Written informed consent/assent to participate was obtained from each participant in the study. Oral informed consent/assent for publication was obtained from all participants.

Conflicts of Interest

The authors declare no conflicts of interest. This manuscript represents the views of the authors and does not necessarily represent the opinion of the French Medicines Agency.

Data Availability Statement

All data produced in the present study are available upon reasonable request to the corresponding authors.

Endnotes

¹ "Pharmacoepidemiology is the study of the use of and the effects of drugs in large numbers of people, [...] it applies the methods of epidemiology to the content area of clinical pharmacology".

² "A research being carried out 'with' or 'by' members of the public".

³ Each item was rated according to a color: (i) Green: presence of the item clearly stated; (ii) Orange: presence of the item but not precisely described; (iii) Red: absence of the item.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.