Patient Reported Outcomes in Influenza Clinical Research: State of the Art and Opportunities

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BACKGROUND

Patient-reported outcomes (PRO) are a class of health-related endpoints that directly depend on feedback received from patients. PRO assess not only quality of life (QoL) but also provide insights on disease symptom severity, impact on functional abilities, emotional state, and treatment satisfaction among others[1,2]

PROs could facilitate healthcare professionals to provide more personalized and holistic approach towards patient care, and could aid healthcare authorities in making informed public health decisions through its use in clinical trials, patient-centered drug and vaccine development[1,9]

Assessing influenza symptoms and the impact of interventions via a range of different PRO instruments could be useful in evaluating the intensity and sudden manifestation of symptoms, which may vary from person to person[3,4]

OBJECTIVES

This study aims to comprehensively review the utilization of patient-reported outcomes (PROs) in influenza research, focusing on available instruments, their measurement characteristics, and regulatory considerations

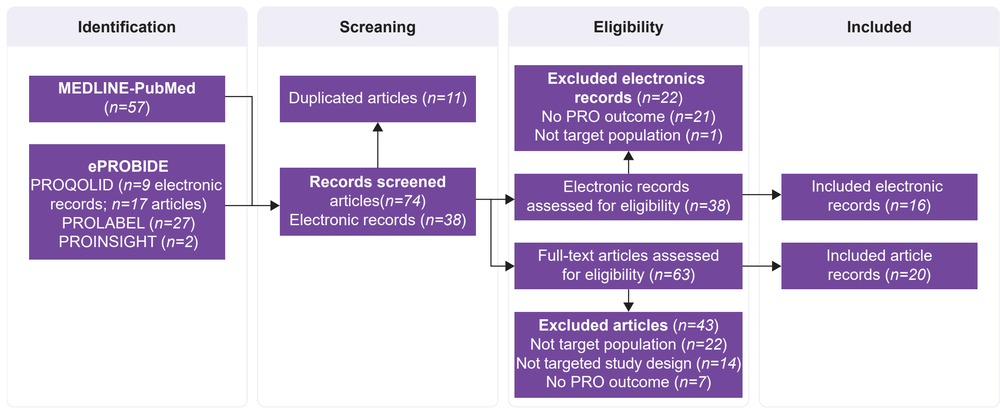
METHODS

- A systematic literature review (SLR) for English records was conducted from June to October 2023 across MEDLINE and the PRO-specific database **ePROVIDE©**, comprising of **three individual databases**:
  - PROINSIGHT© - regulatory body recommendations
  - PROQOLID© - available instruments
  - PROLABELS© - granted product labels
- MeSH terms and keywords were selected for the search algorithms in accordance with the PICO (Population, Intervention, Comparison, Outcome) framework[5]
- Two reviewers (EMM and PMA) conducted independent assessments of all references according to the search eligibility criteria
- The information extracted from the identified articles included, among others: publication year, objective(s), target population, instrument, covered domains, timepoint collection, and principal findings

RESULTS

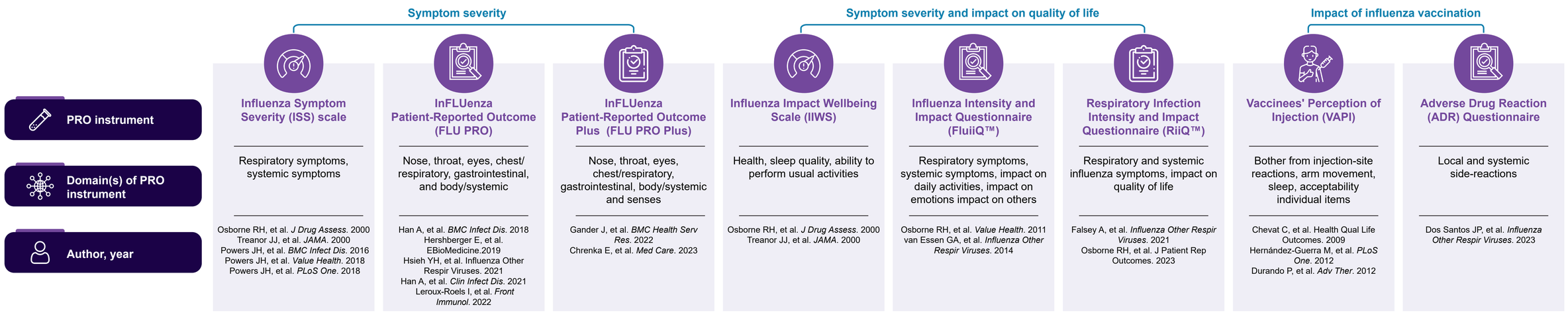
- Out of **101 database** records identified in the SLR, **36 eligible** articles were selected. Among these, **20 articles** document the development, psychometric characteristics or clinical application of influenza-specific PRO instruments aimed at capturing patients' experiences, including symptoms, QoL, and post-vaccination reactogenicity in immunized respondents (**Figure 1**)
- Two **US FDA** regulatory documents were found, suggesting that change in influenza-like-illness symptoms, as measured by PRO, can be a useful secondary endpoint in trials
- Additionally, **product labels** containing PROs in the clinical section were found for **eight** influenza symptomatic therapies
- Literature suggests that vaccination or disease management strategies likely lead to differential PRO results in clinical research studies, which broadly fall into three categories of assessment: influenza symptom severity, influenza symptom severity and the impact on QoL, and patient tolerability of influenza vaccination (**Figure 2**)
- The SLR also reviewed unidentified PROs instruments used in product labels for influenza interventions limited to US FDA and EMA, with the most frequently reported PRO endpoint of interest being time to **improvement or alleviation of influenza**
- Recommendations stemming from this review advocate for increased patient-centricity in clinical decision-making, drug development and surveillance with focus in three identified concepts of interest: Severity and duration of disease symptoms, impact on QoL, and drug tolerability (**Figure 3**)

Figure 1: PRISMA Flow Diagram of Article Selection in the SLR



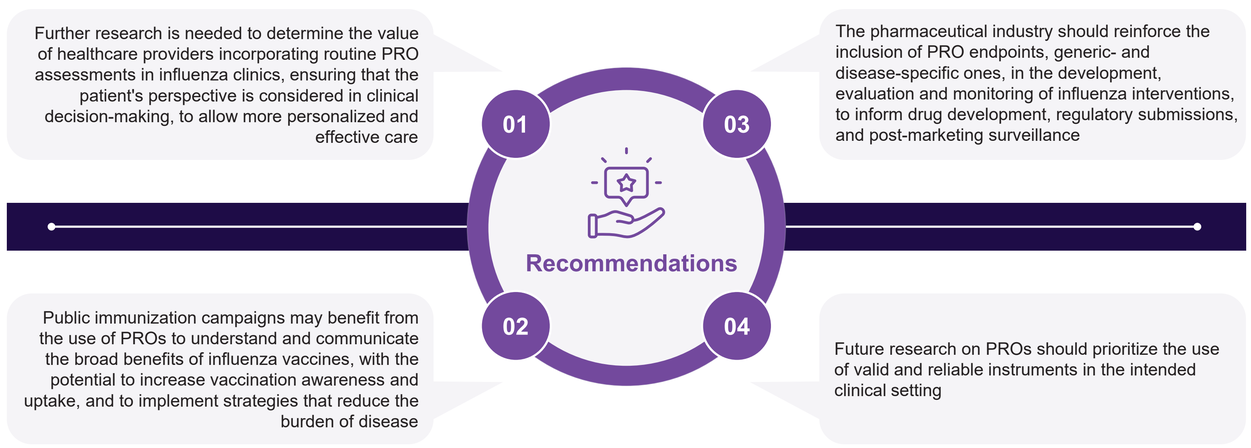
PRO, patient-reported outcome; SLR, systematic literature review

Figure 2: PRO Instruments in Clinical Research



PRO, patient-reported outcome

Figure 3: Author Recommendations Based on the Systematic Review



STRENGTHS

- Early detection of complication of influenza and ILI, including improvement or deterioration in patients
- Continuous monitoring of symptom severity and QoL could provide a holistic understanding of the impact of influenza and vaccinationn[1,2]
- PRO measures of vaccination side reactions can improve the development and uptake of influenza interventions

LIMITATIONS

- Challenges in implementing PROs include the selection of instruments with evidence of acceptable psychometric properties[6,7] in the intended context of use, addressing patient compliance issues, safeguarding privacy, and ensuring equitable access[2]
- Psychometric evidence on available PRO instruments varies in quality and is limited to its underlying clinical setting
- The subjective nature of PROs could introduce biases and confounding factors[8]

CONCLUSION

- PROs provide a unique perspective on the individual's perceived course of influenza and a complementary method for evaluating drug tolerability
- This review offers critical insights for healthcare professionals, researchers, and decision-makers to effectively integrate PROs into research on influenza prophylaxis or symptomatic treatment
- Further studies are required to fully comprehend how PROs may enhance routine care in real-world clinical settings

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ABBREVIATIONS

EMA: European Medicines Agency; ILI: influenza-like-illness; MeSH: Medical Subject Heading PRO: patient-reported outcome; QoL: quality of life; SLR: systematic literature review; US FDA: United states food and drug administration

CONFLICT OF INTEREST

JBHis an employee of Sanofi (a company that develops and commercializes influenza vaccines) and own stocks of the company.
EMM, PMA, BAFM, and CG received consulting fees from Sanofi. RO is the author of the Respiratory Infection, Intensity and Impact Questionnaire (RiiQTM), licensed by Sanofi.

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