Sanguanboonyaphong P, Niamhun N, Yoodee J, Chewaskulyong B, Saeteaw M, Pasukmoon N, Sirichanchuen B. Efficacy and safety of original versus generic erlotinib in non-small cell lung cancer with epidermal growth factor receptor gene mutations in Thailand: a retrospective cohort study Pharmacy Practice 2025 Jul-Sep;23(3):3257.
https://doi.org/10.18549/PharmPract.2025.3.3257.

**Original Research**

# Efficacy and safety of original versus generic erlotinib in non-small cell lung cancer with epidermal growth factor receptor gene mutations in Thailand: a retrospective cohort study

Phitjira Sanguanboonyaphong, Narawadee Niamhun, Jukapun Yoodee, Busyamas Chewaskulyong, Manit Saeteaw, Nonthikun Pasukmoon, Buntitabhon Sirichanchuen

Received (first version): 15-Jul-2024 Accepted: 27-Sep-2024 Published online: 29-Aug-2025

**Abstract**

**Background:** Non-small cell lung cancer (NSCLC) is a major cause of cancer-related mortality, for which mutations in the epidermal growth factor receptor (EGFR) gene are common in Asian populations. Erlotinib, an EGFR tyrosine kinase inhibitor, has been used as the first-line therapy for EGFR-mutated NSCLC. Generic erlotinib has been introduced in Thailand to increase accessibility, but efficacy and safety are major concerns. Objective: This study aimed to compare the efficacy and safety of generic versus originator erlotinib among Thai patients using real-world data from two quaternary hospitals. **Methods:** A retrospective cohort study collected data from medical record of advanced or metastatic EGFR-mutated NSCLC receiving either generic or originator erlotinib between September 2019 and September 2021 from Maharaj Nakorn Chiang Mai Hospital and Sunpasitthiprasong Hospital, Thailand. Primary outcomes were clinical benefit rate (CBR) at 12 months, progression-free survival (PFS) and treatment-related adverse events. Kaplan-Meier survival curve with log-rank test and the propensity score (PS)-adjusted models were employed to estimate the difference of response rate and safety between the generic vs. the originator erlotinib. **Results:** One hundred and seven patients were included. CBR at 12 months of the generic vs. originator erlotinib were 75.4 and 74.0% (adjusted HR 1.47 [95%CI 0.45-4.83, p= 0.519]). Median PFS of the generic vs. originator erlotinib were 15.2 months and 18.9 months (adjusted HR 1.98 [95%CI 0.99-3.94, p = 0.053]). The incidence of any adverse events for the generic vs. originator was 21.0 and 36.0% (adjusted OR 0.84 [95%CI 0.26-2.71, p = 0.770]). Most adverse events comprised mild skin toxicity, with no significant difference between the two groups (adjusted OR 1.03 [95%CI 0.31-3.43, p = 0.958]). **Conclusions:** No significant differences were noted regarding efficacy or safety between generic and originator erlotinib. These findings support the use of generic erlotinib as a cost-effective alternative in Thailand.

**Keywords:** Non-Small Cell Lung Cancer (NSCLC); Epidermal Growth Factor Receptor Genes (EGFR); erlotinib; generic drugs

**Phitjira Sanguanboonyaphong**. PharmD, BCP, BCOP, Lecturer Division of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Ubon Ratchathani University, Ubon Ratchathani 34190 Thailand. phitjira.s@ubu.ac.th
**Narawadee Niamhun**. BPharm, PhD, Assistant Professor, Department of Pharmaceutical Care, Faculty of Pharmacy, Chiang Mai University, Chiang Mai 50200 Thailand,3Northern Thailand Thoracic Oncology Group (NT-TOG), Chiang Mai University, Chiang Mai 50200 Thailand. narawadee.n@cmu.ac.th
**Jukapun Yoodee**. PharmD, BCP, BCOP, Assistant Professor, Department of Pharmaceutical Care, Faculty of Pharmacy, Chiang Mai University, Chiang Mai 50200 Thailand, Center for Medical and Health Technology Assessment (CM-HTA), Department of Pharmaceutical Care, Faculty of Pharmacy, Chiang Mai University, Chiang Mai 50200 Thailand. jukapun.y@cmu.ac.th
**Busyamas Chewaskulyong**. MD, Associate professor, Division of Medical Oncology, Department of Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200 Thailand. busyamas.chewask@cmu.ac.th
**Manit Saeteaw**. BPharm, BCP, BCOP, Assistant Professor, Faculty of Pharmaceutical Sciences, Khon Kaen University, Khon Kaen 40002 Thailand. manitsa@kku.ac.th
**Nonthikun Pasukmoon**. BPharm, MPharm, Pharmacist, Department of Pharmacy, Sunpasitthiprasong Hospital, Ubon Ratchathani 34000 Thailand. Sanooker.warit@hotmail.com
**Buntitabhon Sirichanchuen***. BPharm, PhD, Assistant Professor, Department of Pharmaceutical Care, Faculty of Pharmacy, Chiang Mai University, Chiang Mai 50200 Thailand, Northern Thailand Thoracic Oncology Group (NT-TOG), Chiang Mai University, Chiang Mai 50200 Thailand, Center for Medical and Health Technology Assessment (CM-HTA), Department of Pharmaceutical Care, Faculty of Pharmacy, Chiang Mai University, Chiang Mai 50200 Thailand. buntitabhon.s@cmu.ac.th

## INTRODUCTION

Non-small cell lung cancer (NSCLC) constitutes a significant healthcare burden in Thailand[1], accounting for a substantial portion of cancer-related morbidity and mortality in the region. Among the various molecular subtypes of NSCLC, the presence of epidermal growth factor receptor (*EGFR*) gene mutations has emerged as a critical determinant for targeted therapy.[2] The frequency of the *EGFR* mutation in Asian populations was higher than in Caucasian populations (51.1 vs. 14.6%).[3-4] The response rate of EGFR tyrosine kinase inhibitors (TKI) such as gefitinib or erlotinib in metastatic NSCLC with *EGFR* mutation positive was superior compared with chemotherapy.[5-6]

Erlotinib, a first-generation EGFR TKI, has demonstrated

impressive efficacy in treating *EGFR*-mutated NSCLC, leading to improved outcomes and prolonged survival for affected patients with approximate four months longer in median progression-free survival (PFS) (9.7 months in erlotinib vs. 5.2 months in standard chemotherapy).[7-8] Currently, it constitutes the only EGFR TKI which is accessible in all health beneficial schemes in Thailand. The availability of generic versions of erlotinib has significantly impacted the treatment landscape, aiming to improve drug accessibility and reduce healthcare costs for patients in Thailand.[9] According to the Thai Food and Drug Administration's (TFDA), the regulation of generic drugs in Thailand requires only bioequivalence studies, without clinical equivalence included.[10] The concerns regarding the comparative efficacy and safety of generic erlotinib compared with the original drug have arisen. Because reports indicated the possibility of deviation of response between originator and generic medication, patients with chronic myeloid leukemia (CML) called for quality and consistency when generics were introduced to treat their cancer.[11-13]

To address this crucial clinical question, a retrospective cohort study was conducted to comprehensively evaluate and compare the efficacy and safety of generic and originator erlotinib among Thai patients with *EGFR*-mutated NSCLC. This study used real-world data collected from two quaternary hospitals across Thailand, providing valuable insights into the effectiveness and tolerability of these treatments in a diverse patient population.

## METHODS

### Study design

This retrospective cohort study comprised adult patients newly diagnosed with *EGFR*-mutated advanced or metastatic NSCLC receiving either first-line original or generic erlotinib for at least three months from September 2019 until September 2021 from two hospitals at Maharaj Nakorn Chiang Mai Hospital; university affiliated hospital, Chiang Mai, Thailand as the largest hospital in north of Thailand, and Sunpasitthiprasong Hospital, Ubon Ratchathani, Thailand; as one of the large cancer center in northeast Thailand.. Patients were not in a terminally ill state and exhibited good physical condition, according to the Eastern Co-operation Oncology Group (ECOG) performance status, indicated by one of the following: ECOG performance status 0 to 2 or ECOG performance status 3 to 4 resulting from disease NSCLC not caused by another co-morbidity. Gene mutations detected were sensitive to erlotinib including exon 19 deletion (DEL19), exon 21 substitution mutations (L858R or L861Q) or exon 18 substitution mutations (G719X). Patients whose clinical response, and radiographic laboratory tests, e.g., computerized tomography (CT) or magnetic resonance imaging (MRI) could be assessed. Patients with insufficient data for analysis or switching between original and generic erlotinib would be excluded. Sample size estimation based on the response rate of erlotinib from the EURTAC trial[8] at 71.0% and margin 12.5% with power 80%, alpha = 0.0500 (one-sided) should be 163 patients per group.

### Outcomes

Primary outcomes were clinical benefit response rate (CBR) at 12 months, PFS and treatment-related adverse events. CBR at 12 months was defined as the percentage of patients with completed response, stable disease, partial response or patients without document of failure or continued treatment at 12 months. Failure of treatment was defined when any following events occurred first including disease progression, death from any causes or discontinuation of medication due to severe adverse reactions. The data were collected at least 12 months after the first use of the drug and the data cut-off date was March 2022. Data were extracted from medical records including patient demographics, disease characteristics, treatment regimens, the starting date, the last date of erlotinib, the reasons for drug discontinuation and comorbidity.

### Ethics approval

This retrospective study was conducted in compliance with the principles of the Declaration of Helsinki and was approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University (Approval No. 415/2021) and the Research Ethics Committee, Sunpasitthiprasong Hospital (Approval No. 024/2565). Patient confidentiality and data anonymization were strictly upheld throughout the study to protect the participants' privacy.

### Statistical analysis

Descriptive statistics were used to explain baseline characteristics and outcomes. SPSS, Version 16 was used for statistical analysis. Chi-square and independent t-test were used to compare between the erlotinib originator and its generic. Kaplan-Meier survival curve with log-rank test were also used to compare the PFS between the interventions. The propensity score (PS)-adjusted Cox-proportional hazard model was employed to estimate hazard ratio of response rate between the generic vs. the originator group, while the PS-adjusted logistic regression was used to compare any adverse events and skin-related adverse events of the interventions. PS score was estimated using binary logistic regression with covariates and was applied in the models as a covariate. Age and other variables with p values less than 0.100 in the difference characteristics of patients between groups were used as covariates.

## RESULTS

In this retrospective cohort study, 107 patients were included. The characteristics of patients were well-distributed across groups including age, sex, follow-up time, presentation of underlying diseases, Charlson's comorbidity score and gene mutation. However, a notable disparity emerged in terms of medical benefit insurance, as shown in Table 1**.** Subsequent analyses carefully accounted for this imbalance. Age, health insurance (p value <0.001) and CNS metastasis (p value <0.001) were applied in the PS-adjusted Cox-proportional hazard model. All patients took erlotinib at 150 mg once daily.

**Response rate**

The primary outcomes of this study were to compare the response rate and safety between the erlotinib generic vs. its originator. The CBR at 12 months was 75.4% (63.9-87.0) vs. 74.0% (61.4-86.6) ($p$ = 0.864) in generic and originator, respectively, as shown in Table 2 and Figure 1.

**Table 1.** Characteristics of patients included in this study (n=107)

| Characteristic | Number of patients (percentage) | | P value |
|---|---|---|---|
| | Generic (n=57) | Originator (n=50) | |
| Age (Mean (SD)) | 63.0 (10.4) | 67.0 (11.6) | 0.066 |
| Female | 29 (50.9%) | 29 (58.0%) | 0.461 |
| Follow-up time months (Median (IQR)) | 9.46 (8.0-15.2) | 8.9 (10.9-15.2) | 0.186 |
| Medical benefit insurance | | | |
| - Universal health coverage (UC) | 44 (77.2%) | 9 (18.0%) | <0.001 |
| - Civil Servant Medical Benefit (CSMB) | 10 (17.5%) | 37 (74.0%) | |
| - Social Security scheme (SSS) | 1 (1.8%) | 2 (4.0%) | |
| - Self-payment | 2 (3.5%) | 2 (4.0%) | |
| Underlying disease | | | |
| - No | 40 (70.2%) | 32 (64.0%) | 0.497 |
| - Yes | 17 (29.8%) | 18 (36.0%) | |
| Charlson's comorbidity score (Mean (SD)) | 8.1 (1.2) | 8.5 (1.3) | 0.102 |
| CNS metastasis | | | |
| - No | 38 (66.7%) | 12 (66.7%) | <0.001 |
| - Yes | 6 (10.5%) | 9 (10.5%) | |
| - N/A | 13 (22.8%) | 29 (22.8%) | |
| Gene mutation | | | |
| - Exon18 mutation (G719X) | 2 (3.5%) | 0 | 0.152 |
| - Exon19 deletion | 37 (64.9%) | 23 (46.0%) | |
| - Exon 21 mutation (L585R, L861Q) | 14 (24.6%) | 23 (46.0%) | |
| - Others | 4 (7.0%) | 4 (8.0%) | |

**Table 2.** Clinical benefit response rate, progression free survival and safety outcome

| Outcome | Number of patients (percentage) [95% Confidence interval] | | Hazard ratio or Odds ratio [95% Confidence interval, p value] | |
|---|---|---|---|---|
| | Generic (n=57) | Originator (n=50) | Unadjusted | Adjusted |
| CBR at | 43 (75.4%) | 37 (74.0%) | 1.08[a] | 1.47[a] |
| 12 months | 63.9-87.0 | 61.4-86.6 | 0.45-2.58, p=0.864 | 0.45-4.83, p= 0.519 |
| Progression free survival | 15.2 months | 18.9 months | 1.28[a] | 1.98[a] |
| | 9.0-23.6 | 9.7-23.1 | 0.72-2.17, p = 0.435 | 0.99-3.94, p = 0.053 |
| Any | 12 (21.0%) | 18 (36.0%) | 0.47[b] | 0.84[b] |
| adverse events | 11.4-33.9 | 22.9-50.8 | 0.20-1.12, p = 0.089 | 0.26-2.71, p = 0.770 |
| Grade 3-4 | 2 (3.5%) | 1 (2.0%) | 1.78[b] | 3.65[b] |
| adverse event | 0.4-12.1 | 0.0-10.6 | 0.16-20.26, p=0.641 | 0.14-92.08, p=0.432 |
| Skin-related | 12 (21.0%) | 16 (32.0%) | 0.57[b] | 1.03[b] |
| adverse events | 11.4-33.9 | 19.5 - 46.7 | 0.24-1.35, p = 0.201 | 0.31-3.43, p = 0.958 |

CBR: Clinical benefit response rate
[a]Reported as hazard ratio with its corresponding 95% confidence interval
[b]Reported as odds ratio with its corresponding 95% confidence interval
Note: Adjusted by propensity score which contained age, sex, and health insurance

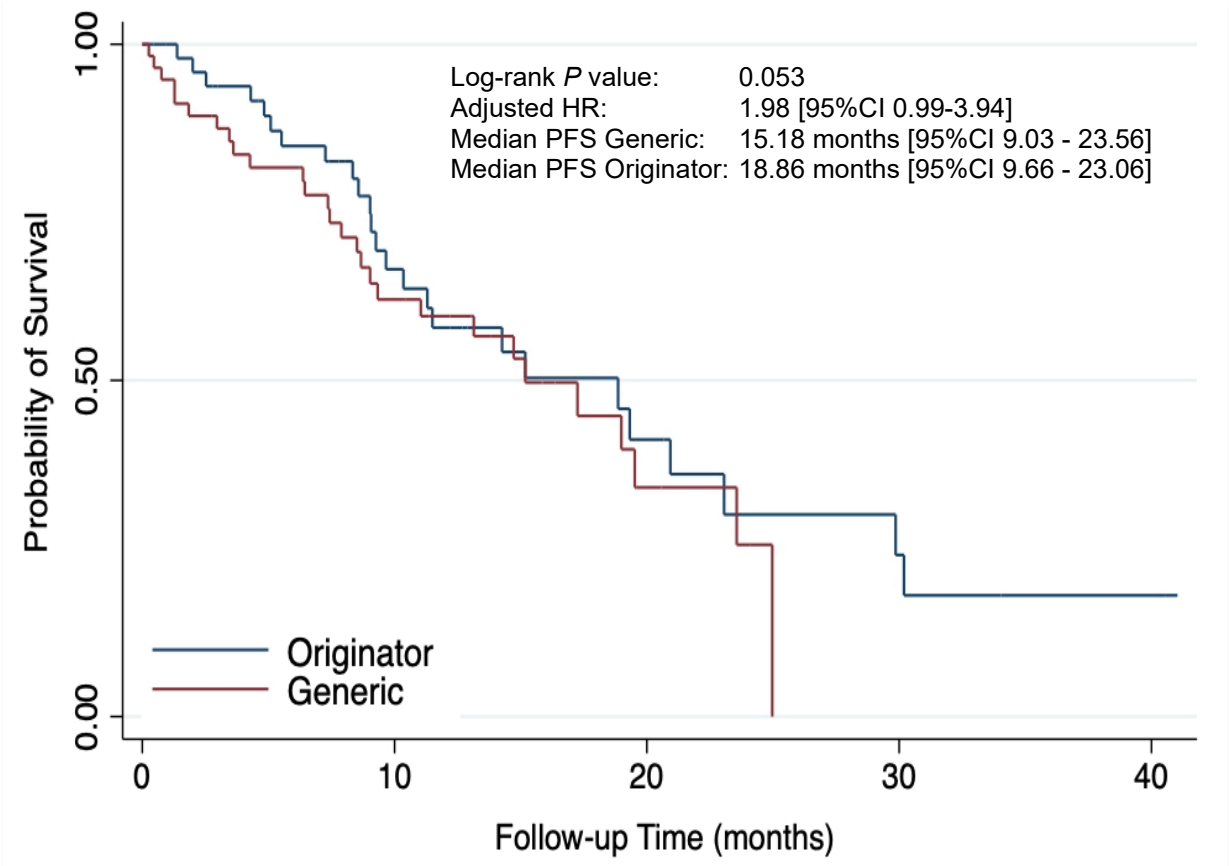


**Figure 1.** Kaplan-Meier plot of progression-free survival

**Safety**

The incidence of any adverse events occurred among 12 patients (21.0%) and 18 patients (36.0%) in the generic vs. the originator group. The odds ratio of any adverse event was 0.47 [95%CI 0.20-1.12, p = 0.089]. The adverse events observed were mostly grade 1/2 skin toxicity; acneiform rash, paronychia, dry skin and pruritus which occurred among 12 patients (21.0%) and 16 patients (32.0%) in the generic vs. the originator group (p = 0.089). There was no record of dose reduction. However, three patients were discontinued from erlotinib treatment due to adverse events, totaling two patients in the generic group (grade 3 acne-like rash and unindicated) and one patient in the original group (severe dyspnea). The odds ratio of grade 3 adverse event was 1.78 [95%CI 0.16-20.26, p=0.641], as shown in Table 2.

## DISCUSSION

The standard treatment of advanced or metastatic NSCLC with sensitive *EGFR* mutation is EGFR TKI, namely, erlotinib. After availability of generic erlotinib, this is the first study in Thailand to report the efficacy and safety between generic and originator erlotinib. This study used real-world data from two major hospitals in Thailand, providing valuable insights into the performance of generic cancer treatments in diverse clinical settings and enhancing the relevance of the findings for healthcare practitioners.

**Characteristics of patients in study vs. real life or other studies**

Regarding the characteristic of patients, this study found the majority patients were female (54.2%) and the mean age at diagnosis was 63.0 ± 10.4 and 67.0 ± 11.6 years in the generic group and the originator group, respectively. These characteristics were consistent with related reports of Rosell and colleagues[8] revealing that most patients were female (67.0%) with mean age was 63.4 ± 11.0 years. In addition, this study showed that most patients did not have an CNS metastasis at diagnosis (66.7%) and the most common sensitive mutation were exon 19 deletion and exon 21 mutation which were observed in 64.9 and 24.6% of patients, respectively. These results agreed with the results from Rosell R and colleagues[8] and Zhou C and colleagues.[15]

**Response rate**

In this study, the one-year CBR did not significantly differ for either the patients treated with generic or originator of which were 75.4 and 74.0%, respectively. Correlatedly, the response rate was consistent with the related study and was observed in 71.0% (EURTAC trial).[8] In addition, a median PFS in the generic group was 15.18 months and 18.86 months in the originator group. This did not differ significantly (HR 1.28 [95%CI 0.72 –

2.17; p = 0.435)] and was concordant with the related study (OPTIMAL trial)[14] as median PFS was observed in 13.1 month among patients treated with erlotinib. Interestingly, this study found median PFS was slightly higher than that in the EURTAC study indicating median PFS was 9.7 months. To the best of our knowledge, the prevalence of *EGFR* sensitizing mutation was outstanding in Asian populations compared with that of non-Asian populations. This discrepancy might have stemmed from a different ethnicity which was included in their studies. In one related study[15-16], progression free survival was observed significantly longer among Asian patients receiving *EGFR*-TKIs (HR 0.66 [95%CI 0.48 – 0.91; p = 0.01]). Currently, clinical practice involves using generic erlotinib instead of originator due to patients' affordability. Therefore, to ensure the efficacy of these medicines, this study compared progression free survival showing no difference between the generic and originator (HR 1.95 [95%CI 0.99 – 3.54; p = 0.053]), indicating the efficacy war similar.

**Safety**

In this study, no new adverse events were reported. The most common adverse event was skin toxicity totaling 21.0% in the generic group and 32.0% in the originator group. Interestingly, skin toxicity in this study was lower than that reported by EURTAC[8], OPTIMAL[14] and ENSURE[17] (67.0–73.0% vs. 21.0–32.0%). This disagreement might have been due to a retrospective study leading to an underestimation incidence of adverse events. However, two patients discontinued the treatment due to a grade 3, acne-like rash in the generic group which was compatible with the related reported by the ENSURE study of which seven patients also had grade 3 skin rash. Moreover, this study found one patient left the originator group due to severe dyspnea. Nevertheless, severe dyspnea was not reported from the related studies (EURTAC[8], OPTIMAL[14] and ENSURE[17]). This disparity might be from a patient's disease or erlotinib-induced pneumonitis. According to the limitation of this retrospective study, we could not retrieve further information to clarify the cause of this discontinuation.

The study demonstrates that generic erlotinib offers comparable efficacy and safety to the originator drug for patients with EGFR-mutated NSCLC, supporting its use as a first-line treatment, particularly in resource-limited settings. Generic erlotinib improves accessibility without compromising quality, emphasizing the need for regular outcome monitoring and early detection of adverse events. The findings also highlight the importance of integrating cost-effective generics into national health programs to optimize healthcare expenditures. Policymakers should prioritize centralized procurement, stringent quality regulations, and post-marketing surveillance to enhance confidence in generics and improve access to affordable cancer therapies.

However, this study encountered a few limitations. Firstly, missing data were noted such as ECOG performance status, smoking status and adherence, which might have been an underestimation of adverse events resulting from the retrospective study design. Second, adverse events from oral tyrosine kinase inhibitors could occur at home and be manageable. Thus, spontaneous adverse drug events were unreported leading to an underestimation of adverse events. Furthermore, a small sample size might have been difficult to identify a statistically significant outcome. Although the calculated sample size was 163 patients per group, we included all available patients meeting the inclusion criteria. Ultimately, 57 patients were enrolled in the generic group and 50 patients in the originator group. The limited sample size may be attributed to the relatively low prevalence of *EGFR*-mutated NSCLC diagnosis and patient loss to follow-up during the COVID-19 pandemic. Nevertheless, this study results were confirmed by adjusting the confounding factors and affecting the primary outcomes. To address the limitation of this study, we recommend conducting a prospective investigation to comprehensively evaluate the association between risk factors and survival outcomes. Future studies should include a larger sample size, incorporate multicenter participation to enhance generalizability, and extend the follow-up period to more accurately assess overall survival.These improvements will provide a deeper understanding of the factors influencing survival amd inform more robust clinical decision making. Lastly, the specific brands of generic erlotinib were undisclosed in this study, as these drugs were procured through a centralized medicine procurement system managed by Thailand's National Health Security Office (NHSO). Nonetheless, all generic medications procured must adhere to the Thai FDA's quality standards for generic drug regulation.[10]

## CONCLUSION

This study provides evidence-based insights into the clinical relevance of generic erlotinib in Thai patients with *EGFR*-mutated NSCLC, showing no significant differences in efficacy or safety compared to the originator. These findings support the use of generic erlotinib as a cost-effective alternative, particularly in resource-limited settings. Healthcare providers can improve accessibility without compromising quality, with a focus on monitoring outcomes and managing adverse events like skin toxicity. Additionally, integrating generics into national health programs, enforcing quality standards, and implementing post-marketing surveillance are crucial to optimizing healthcare expenditures and expanding access to affordable cancer therapies.

## AUTHORS CONTRIBUTION

P.S. and B.S. contributed to the study conceptualization. P.S., N.N., J.Y., M.S. and B.S. designed the methodology. Material preparation and data collection was performed by P.S., N.P., B.C. and N.S. Analysis was performed by P.S. and B.S. P.S., N.N., J.Y., B.C., M.S. and B.S. discussed the results. P.S. and B.S. prepared the original manuscript. All authors commented on previous versions of the manuscript. All authors read and approved of the final manuscript.

## CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

## References

1. Lam WY, Fresco P. Medication Adherence Measures: An Overview. Biomed Res Int. Hindawi Publishing Corporation; 2015;2015. PMID: 26539470
2. Leporini C, De Sarro G, Russo E. Adherence to therapy and adverse drug reactions: Is there a link? Expert Opin Drug Saf. 2014;13(SUPPL. 1):41–55. PMID: 25171158
3. Zurita-Cruz JN, Manuel-Apolinar L, Arellano-Flores ML, Gutierrez-Gonzalez A, Najera-Ahumada AG, Cisneros-González N. Health and quality of life outcomes impairment of quality of life in type 2 diabetes mellitus: A cross-sectional study. Health Qual Life Outcomes. Health and Quality of Life Outcomes; 2018;16(1). PMID: 29764429
4. Iljaz R, Brodnik A, Zrimec T, Cukjati I. E-Healthcare For Diabetes Mellitus Type 2 Patients - A Randomised Controlled Trial In Slovenia. Zdr Varst. 2017;
5. Fitria N, Husnia K, Ananta FT, Sari YO. The effect of pillbox use in increasing patients ' adherence to type 2 diabetes mellitus therapy in Lubuk Kilangan health center. Pharm Pract (Granada) [Internet]. 2023;21(4):1–5. Available from: https://doi.org/10.18549/PharmPract.2023.4.2904
6. Febriyanti AP, Tahar N, Badriani B, Dhuha NS, Wahyudin M, Khaerani K, Leboe DW. A Comparative Study to Enhance Medication Adherence: Pillbox vs Medication Reminder Chart. Proc Int Pharm Ulul Albab Conf Semin. 2021;1:26.
7. Ernawati I, Lubada EI, Lusiyani R, Prasetya RA. Association of adherence measured by self-reported pill count with achieved blood pressure level in hypertension patients: a cross-sectional study. Clin Hypertens. 2022 Apr;28(1):12. PMID: 35422008
8. Seuring T, Marthoenis, Rhode S, Rogge L, Rau H, Besançon S, Zufry H, Sofyan H, Vollmer S. Using peer education to improve diabetes management and outcomes in a low-income setting: a randomized controlled trial. Trials. 2019 Sep;20(1):548. PMID: 31477164
9. Fitria N, Sari YO, Putry AR, Putrizeti F, Sukma A. Future challenge on probiotics uses from fermented milk on the endocrine disorder in human. IOP Conf Ser Earth Environ Sci 888(1)012047 DOI 101088/1755-1315/888/1/012047. IOP Publishing Ltd; 2021 Nov 15;888(1):1–7.
10. Fitria N, van Asselt ADIADI, Postma MJMJMJ. Cost-effectiveness of controlling gestational diabetes mellitus: a systematic review. Eur J Heal Econ. Springer Berlin Heidelberg; 2019;20(3):407–417. PMID: 30229375
11. International Diabetes Federation. International Diabetic Federation Diabetic Atlas 10th edition. International Diabetes Federation (IDF). 2021.
12. Sari YO, Fitria N, Mariza W, Lailiani R, Permatasari D. Application of Home Medication Review ( HMR ) on Patient Adherence in Type 2 Diabetes Mellitus ( T2DM ) Blood Sugar Management. 2022;160–167.
13. Schwartz JK. Pillbox use, satisfaction, and effectiveness among persons with chronic health conditions. Assist Technol. United States; 2017;29(4):181–187. PMID: 27689861
14. Bolarinwa OA. Sample size estimation for health and social science researchers: The principles and considerations for different study designs. Niger Postgrad Med J. Nigeria; 2020;27(2):67–75. PMID: 32295935
15. Fitria N, Febiana D, Akram M, Yosmar R. Aspirin-clopidogrel combination therapy for ischemic stroke patients : Clinical efficacy and. Narra J. 2024;4(2):1–10.
16. Bartlett Ellis RJ, Ganci A, Head KJ, Ofner S. Characteristics of Adults Managing Vitamins/Supplements and Prescribed Medications-Who Is Using, Not Using, and Abandoning Use of Pillboxes?: A Descriptive Study. Clin Nurse Spec. United States; 2018;32(5):231–239. PMID: 30095522
17. Mehdinia A, Loripoor M, Dehghan M, Heidari S. The Effect of Pillbox Use on Medication Adherence Among Elderly Patients: A Randomized Controlled Trial. Int Electron J Med. 2020;9(1):38–43.
18. Graetz I, Hu X, Kocak M, Krukowski RA, Anderson JN, Waters T, Curry A, Paladino AJ, Stepanski E, Vidal GA, Schwartzberg LS. A randomized controlled trial of a mobile app and tailored messages to improve outcomes among women with breast cancer receiving adjuvant endocrine therapy. J Clin Oncol. 2023;41(16_suppl):512–512.
19. Hudani ZK, Rojas-Fernandez CH. A scoping review on medication adherence in older patients with cognitive impairment or dementia. Res Social Adm Pharm. United States; 2016;12(6):815–829. PMID: 26797263
20. Miguel-Cruz A, Felipe Bohórquez A, Aya Parra PA. What does the literature say about using electronic pillboxes for older adults? A systematic literature review. Disabil Rehabil Assist Technol. England; 2019 Nov;14(8):776–787. PMID: 30451543
21. Choi EPH. A Pilot Study to Evaluate the Acceptability of Using a Smart Pillbox to Enhance Medication Adherence Among Primary Care Patients. Int J Environ Res Public Health. 2019 Oct;16(20). PMID: 31627440
22. Gast A, Mathes T. Medication adherence influencing factors-an (updated) overview of systematic reviews. Syst Rev. England; 2019 May;8(1):112. PMID: 31077247
23. Jankowska-Polańska B, Karniej P, Polański J, Seń M, Świątoniowska-Lonc N, Grochans E. Diabetes Mellitus Versus Hypertension—Does Disease Affect Pharmacological Adherence? Front Pharmacol. 2020;11(August):1–9.
24. Said AH, Rahim ISA, Zaini NNBM, Nizam NIBS. Factors Affecting Adherence to Lipid-lowering Drugs: A Scoping Review. Oman Med J. 2023;38(4).
25. Fitria N, Sari YO, Ananta FT, Husnia K. Adherence Assessment on Hypertension Therapy Using The Pill Count Method in Lubuk

Kilangan Health Center , Indonesia. J Sains Farm Klin. 2023;69–75.
26. Raparelli V, Proietti M, Romiti GF, Lenzi A, Basili S. The Sex-Specific Detrimental Effect of Diabetes and Gender-Related Factors on Pre-admission Medication Adherence Among Patients Hospitalized for Ischemic Heart Disease: Insights From EVA Study. Front Endocrinol (Lausanne). Switzerland; 2019;10:107. PMID: 30858826
27. Rattanapiratanon A, Kongsomboon K, Hanprasertpong T. Efficacy of a 28-compartment pillbox for improving iron supplement compliance in healthy pregnant women: a randomised controlled trial. J Obstet Gynaecol J Inst Obstet Gynaecol. England; 2021 Nov;41(8):1210–1215. PMID: 33645407
28. Andanalusia M, Nita Y, Athiyah U. The effect of pillbox use and education by pharmacist toward medication adherence in diabetes mellitus patients in a Primary Health Care Center in Mataram. J Basic Clin Physiol Pharmacol. Germany; 2021 Jun;32(4):577–582. PMID: 34214347
29. Fitria N, Idrus L, Putri AR, Sari YO. The usability testing of the integrated electronic healthcare services for diabetes mellitus patients during the pandemic in Indonesia. Digit Heal. United States; 2023;9:20552076231173228. PMID: 37152237
30. Fitria N, Wulansari S, Sari YO. Potential Interactions Analysis of Antihypertensive Drugs Used in Geriatric. Int J Appl Pharm. 2023;15(Special Issue 1):29–33.
31. Arifin B, Idrus LR, van Asselt ADI, Purba FD, Perwitasari DA, Thobari JA, Cao Q, Krabbe PFM, Postma MJ. Health-related quality of life in Indonesian type 2 diabetes mellitus outpatients measured with the Bahasa version of EQ-5D. Qual Life Res. Springer International Publishing; 2019;28(5):1179–1190. PMID: 30649698
32. Choudhry NK, Isaac T, Lauffenburger JC, Gopalakrishnan C, Lee M, Vachon A, Iliadis TL, Hollands W, Elman S, Kraft JM, Naseem S, Doheny S, Lee J, Barberio J, Patel L, Khan NF, Gagne JJ, Jackevicius CA, Fischer MA, Solomon DH, Sequist TD. Effect of a Remotely Delivered Tailored Multicomponent Approach to Enhance Medication Taking for Patients With Hyperlipidemia, Hypertension, and Diabetes: The STIC2IT Cluster Randomized Clinical Trial. JAMA Intern Med. United States; 2018 Sep;178(9):1182–1189. PMID: 30083727
33. Alikari V, Tsironi M, Matziou V, Tzavella F, Stathoulis J, Babatsikou F, Fradelos E, Zyga S. The impact of education on knowledge, adherence and quality of life among patients on haemodialysis. Qual life Res an Int J Qual life Asp Treat care Rehabil. Netherlands; 2019 Jan;28(1):73–83. PMID: 30178430
34. Tan JP, Cheng KKF, Siah RCJ. A systematic review and meta-analysis on the effectiveness of education on medication adherence for patients with hypertension, hyperlipidaemia and diabetes. J Adv Nurs. England; 2019 Nov;75(11):2478–2494. PMID: 30993749