# Study Protocol with Statistical Analysis Plan (SAP)

**Official Title:** Impact of a Pharmacist-Led Education Program on Medication Adherence and Treatment Effectiveness of Direct Oral Anticoagulants in Patients with Atrial Fibrillation: A Randomized Controlled Trial (PharmAD-AF)

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# Impact of A Pharmacist-Led Education Program on Medication Adherence and Treatment Effectiveness of Direct Oral Anticoagulants in Patients with Atrial Fibrillation: A Randomized Control Trial

## SPECIFIC AIMS

The goal of this study is to evaluate the impact of a pharmacist-led education program on patients' medication adherence and treatment outcomes in patient with atrial fibrillation (AF) newly prescribed direct oral anticoagulants (DOACs) for stroke prevention. In addition, we aim to understand patients' medication use behavior by comparing self-reported data and administrative claims data, and to explore the potential utility of DOAC blood concentration as a biomarker for medication adherence and treatment outcomes.

We propose a five-year project to evaluate the effectiveness of a pharmacist-led education program on patients' medication adherence and treatment outcomes by a pragmatic, randomized control trial. We will collect data on medication use behavior, including medication adherence and refill adherence, as well as DOAC blood concentration during follow-up. In addition to primary data collection, we will also utilize currently available data sources, including electronic medical records and administrative claims data, to understand patients' baseline characteristics and to assess treatment outcomes. We will achieve our study goal by completing the following aims:

**Aim 1: To evaluate the impact of a pharmacist-led patient education program on patients' medication adherence and treatment outcomes.**

The primary endpoint of this pragmatic trial is medication adherence. Patients diagnosed with AF who are newly prescribed DOACs for stroke prevention will be recruited into the trial. Eligible patients will be randomized into the intervention group and the control group. In the intervention group, patients will receive one-time patient education from a clinical pharmacist or a well-trained senior Pharm.D. students at the time of the initial prescription of DOACs. Two follow-up visits with the clinical pharmacist will be scheduled for patients in the intervention group to further reconcile issues related to DOAC use and monitor laboratory tests. Patients in the control group will receive usual care. DOAC adherence will be measured at patients' three-month and six-month follow-up visits to the physician, using the Adherence to Refills and Medications Scale (ARMS). The mean ARMS score will be compared between the intervention and the control groups.

The secondary endpoint of this trial is treatment outcomes, including effectiveness and safety events. We will capture the one-year and two-year thromboembolic and bleeding events following the DOAC therapy initiation using the National Health Insurance (NHI) claims data. Effectiveness will be measured by systemic thromboembolic events, and safety will be measured by major bleeding events. The event rates will be compared between the intervention group and the control group.

*Hypothesis: We hypothesize that the pharmacist-led education program will improve patients' medication adherence and treatment outcomes.*

**Aim 2: To understand patients' DOAC usage behavior by comparing self-reported data and administrative claims data.**

The second part of this study aims to provide a comprehensive understanding about patients' medication use behavior, including medication adherence and refill adherence. Self-reported medication and refill adherence will first be report descriptively. We will next explore the reasons for non-adherence by assessing patients' response to each of the eight questions that measure medication adherence in the ARMS. Understanding the reasons for non-adherence will help us to refine our education program by providing additional explanations or education materials on factors contributing to poor adherence.

In addition, we will compare self-reported medication and refill adherence from the ARMS to the pharmacy records from the NHI claims data. In the claims data, medication adherence will be measured

by proportion of day covered (PDC) during three and six months of follow-up, and refill adherence will be measured as number of refills during three and six months of follow-up. Given the easy access and low copayment of pharmaceutical care, we anticipate observing a discrepancy between medication adherence and refill adherence. Specifically, we expect a high prescription refill rate for both the intervention and the control groups but suboptimal medication adherence in the control groups.

**Aim 3: To explore the potential utility of DOAC blood concentration as a biomarker for medication adherence and treatment outcomes.**

Because of the predictable pharmacokinetic and pharmacodynamic profiles, DOACs do not require routine blood monitoring. While the lack of requirement for monitoring blood concentrations is one of the advantages of DOACs, the absence of data on blood concentration also contributes to the uncertainty in therapeutic monitoring of DOACs. DOAC testing and monitoring may be necessary for certain patients, such as those who with low adherence or at critical conditions.[1] We therefore aim to provide further evidence on the correlation between DOAC concertation and medication adherence and treatment outcomes.

At the three-month and six-month follow-up physician appointments, in addition to assessing medication adherence, we will also measure patients' DOAC trough concentration. The proportion of patients with blood concentration in the expected range will be compared between the intervention and the control groups. We will also evaluate the correlation between patients' self-reported medication adherence and their DOAC blood concentration.

Finally, we will evaluate the association of DOAC blood concentration with the treatment outcomes as proposed in Aim 1. Both effectiveness and safety events will be assessed. We expect to see that a higher proportion of patients in the control group displays low DOAC concentration compared to the intervention group. In addition, the occurrence of thromboembolic events is more frequent in the control group compared to the intervention group.

Together, these three aims will provide a comprehensive evaluation on the effectiveness of the pharmacist-managed education program on patient care, further enhance our understanding on patients' medication use behavior, and advance our knowledge on pharmacokinetic and clinical management of DOACs. To the best of our knowledge, this will be the first study that evaluates the impact of a pharmaceutical care program by a pragmatic trial in Taiwan.

## BACKGROUND AND SIGNIFICANCE

AF is the most common type of arrhythmia, characterized by irregular contractions of the atria due to abnormal electrical impulses. Individuals with AF face a 4 to 5-fold increased risk of ischemic stroke compared to those without AF.[2,3] DOACs are the first line therapy for stroke prevention for patients with AF.[4,5] DOACs have been shown to be effective in stroke prevention and with a lower risk of bleeding compared to the warfarin.[6-9] In addition, unlike warfarin, DOACs do not require regular laboratory monitoring and have fewer complicated drug interactions,[10] which makes them the preferred therapeutic choice. Despite of the therapeutic advantages of DOACs, ensuring patient adherence remains crucial for optimizing the effectiveness and safety of DOAC therapy. DOACs adherence has been reported to be suboptimal; one-third of the patients had adherence <80%.[11] A Taiwanese study also found that adherence to DOACs was not better than that to warfarin.[12] Non-adherence to DOACs is associated with an increased risk of thromboembolism and bleeding.[13,14]

One way to improve patient adherence is through patient education. It has been reported that pharmacist-led anticoagulation clinic (ACC) services can improve the quality of warfarin therapy and reduce thromboembolic and bleeding events.[15] However, there is limited evidence regarding the impact of pharmacist-led ACC services on DOAC therapy. An U.S. study demonstrated that pharmacist-led interventions, such as providing ACC services and tailoring monitoring frequency, were associated with improved DOAC adherence.[16] Another study from China demonstrated that pharmacist-led remote monitoring of DOAC therapy via telephone during the COVID-19 pandemic resulted in reduced bleeding incidents and hospital readmissions.[17] While these two studies provide some data on the effectiveness of

pharmacist-led interventions on patients adherence and outcomes, the evidence is still preliminary. Based on our understanding, there is currently no studies investigating the reasons behind DOAC non-adherence in Taiwan. Understanding the reasons for poor medication adherence is essential for establishing and refining an effective medication education program. Further assessment of the effectiveness of pharmacist-led interventions with a robust study design and comprehensive evaluation is needed.

Our study is prominent and innovative because of the following reasons. To our knowledge, this will be the first pragmatic, randomized control trial that evaluates the impact of a pharmacist-led patient education program on patients' adherence on DOACs and treatment outcomes in Taiwan. Through the experimental design, our study results will be more robust than the previous findings, providing more solid evidence on pharmacist-led health services. The one-time health education intervention used in this study can be easily applied to other situations, making it adaptable in various pharmacotherapy scenarios. In addition, the pragmatic design of this study ensures that our findings are applicable to real-world settings, holding direct clinical and policy application value. As mentioned earlier, this study will be the first to investigate the reasons for DOAC non-adherence in Taiwan. This information will not only help tailor the design of our intervention program but also improve the design of future medication education programs. Finally, our study is innovative because it will be the first study that correlates DOAC blood concentration and medication use behavior. Unlike warfarin, which can be monitored by international normalized ration (INR), common therapeutic monitoring tests for DOACs are unreliable. It is therefore especially important to understand the potential role of DOAC blood concentration as a potential biomarker for DOAC therapeutic monitoring. Our study will fill the current gap in evidence by providing further insight into the association between DOAC blood concentration and treatment outcomes.

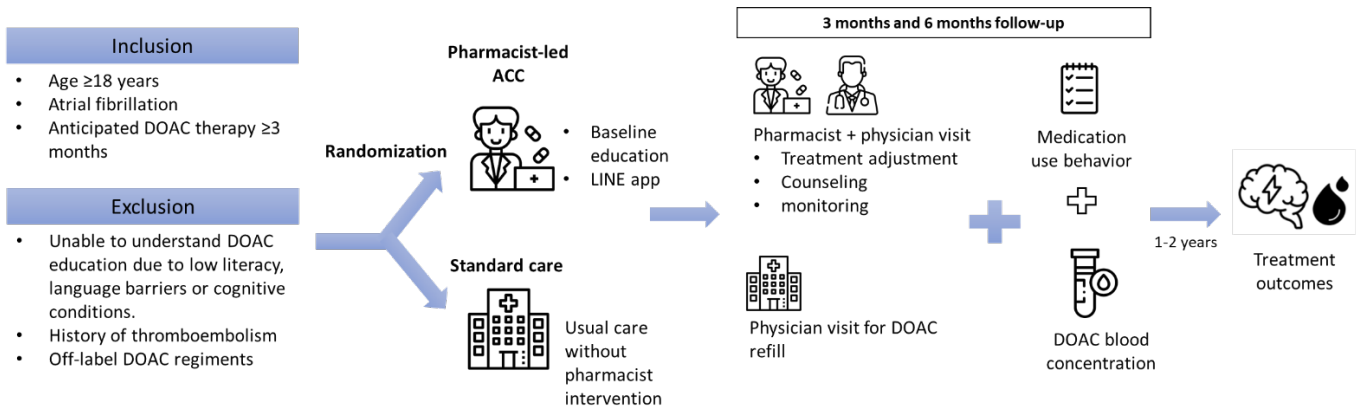
## RESEARCH DESIGN AND METHODS

### Study Design and Setting

This two-arm, pragmatic, randomized control trial will be conducted at National Taiwan University Hospital (NTUH), a tertiary medical center located in Taipei, Taiwan. Two data sources will be utilized in this study: the electronic medical records (EMRs) from the NTUH and the NHI claims data from the Health and Welfare Database. The NTUH EMRs will be used for patients' baseline assessment and screening for eligibility. The NHI claims data will be used for event follow-up and medication use behavior assessment.

Patients who are newly prescribed DOACs for stroke prevention will be recruited from outpatient clinics of the NTUH. Eligible patients who are randomized to the intervention group will be referred to a pharmacist-led ACC for patient education. The NTUH ACC was established in 2012, and is operated by two clinical pharmacists. The ACC provides comprehensive education and follow-up services for patients under oral anticoagulant therapy (both warfarin and DOAC). The ACC has been providing high-quality services to over 1,000 patients; more than 80% of the warfarin users achieved their therapeutic goals after the pharmacists' intervention. Figure 1 below provides an overview of the study design and process.

**Figure 1. Graphical illustration of study design and process**




DOAC: direct oral anticoagulant.

## Study Population and Randomization

In this trial, we will include patients with AF who are newly initiate DOAC therapy for stroke prevention. Patients who are 18 years or older, with an AF diagnosis, and are expected to receive DOAC therapy for at least three months for stroke prevention will be recruited. Patients will be excluded if they are illiterate, have cognitive impairment, receive off-label DOAC regimens, or are pregnant or breastfeeding.

Patients will be recruit from the NTUH outpatient clinics. We will collaborate with two attending physicians at the NTUH who will help to screen the potential study subjects. Those patients will be referred to the research team for further evaluation of the eligibilities. Patients eligible to the trial will be randomized in a 1:1 ratio into the intervention and the control groups. Patients in the intervention group will receive a baseline DOAC education intervention by a clinical pharmacist or a well-trained senior Pharm.D. student at the ACC. Participants in the study and pharmacists providing care will be aware of the intervention assignment. The principal investigator will be blinded until the end of the trial when all follow-up data are collected, and remain blinded for data analysis.

We plan to recruit a total of 400 patients for this study, with 200 for primary prevention and 200 for secondary prevention. We will first stratify patients by their level of prevention (i.e., primary and secondary) and then randomize them into the intervention and the control groups. The sample size was estimated using G*Power software.[18,19] The required sample size was 128 to detect a moderate effect in adherence, with a power of 0.80 and a significance level of 0.05. Given that the effect of the pharmacist-led intervention will be evaluated separately for DOAC primary and secondary prevention, we propose recruiting 200 patients for each group, resulting in a total of 400 patients.

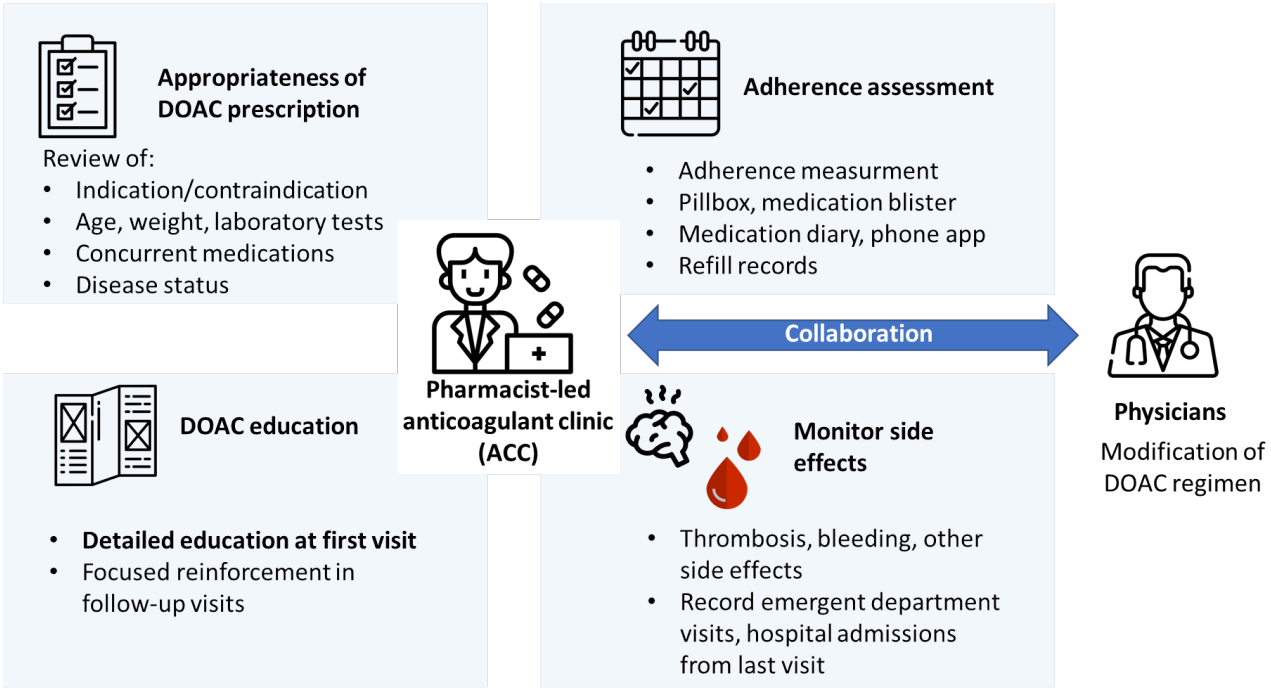
## Intervention

Patients in the intervention group will be referred to the pharmacist-led ACC. At the first ACC visit, a comprehensive DOAC education will be provided, including information on (1) the indication and the reason of DOAC prescription, (2) the name and the appearance of the DOAC agent, (3) the dose, frequency, time of administration, (4) the mechanism of action, (5) management of missed doses, (6) potential side effects and self-monitoring, and (7) perioperative management. Patients will receive an education leaflet about DOACs to improve their understanding. An example of the DOAC education leaflet is provided in Figure 2.

**Figure 2. Example of DOAC education leaflet**


In addition to the education leaflet, patients will receive a pillbox and a medication diary to help improve adherence to DOACs. They will also be encouraged to join the official ACC LINE app account for prompt consultation regarding drug-related issues, such as missed doses, side effects, and planned procedures. The pharmacist will also arrange two follow-up ACC visits, one at three months and the second at six months after the first visit. At the baseline ACC visit, the pharmacist will review patients' EMRs to ensure an on-labeled DOAC dose regimen is prescribed. If the regimen is incorrectly prescribed, the pharmacist will contact the physician for prescription adjustment. During the follow-up visits, the pharmacist will identify any changes in laboratory tests and concurrent medications between the two visits. If there are drug related problems, the pharmacist will contact the prescribers for adjustments. The key components of the pharmacist-led ACC services are provided in Figure 3.

**Figure 3. Key components of the pharmacist-led anticoagulant clinic services**




DOAC: direct oral anticoagulant.

## Study Endpoints

The primary endpoint of this study is medication adherence, measured by the ARMS. The ARMS is a 12-item scale, with eight items measuring medication-taking adherence and four items measuring refill adherence.[20] The items are structured using a 4-point Likert scale to assess the frequency of missed doses or refills, ranging from 1 "none of the time", 2 "some of the time", 3 "most of the time", to 4 "all of the time". A higher ARMS score indicates a lower adherence. The ARMS has good internal consistency and test–retest reliability, and it has been shown to be strongly correlated with the medication-taking and refill adherence.[20] The ARMS will be administered to all study participants at their three-month and six-month physician follow-up appointments as shown in Figure 1.

The secondary endpoint is the treatment outcomes, including effectiveness and safety. Effectiveness will be measured by systemic thromboembolism, which are ischemic stroke (IS), transient ischemic attack (TIA), myocardial infarction (MI), coronary artery disease (CAD), peripheral artery disease (PAD), and venous thromboembolism (VT). Safety will be measured by major bleeding, which are intracranial hemorrhage (ICH), gastrointestinal bleeding (GIB), and other major bleeding events. Clinical events will be measured at one-year and two-year follow-up by the NHI claims data, defined as inpatient admissions with a primary discharge diagnosis code corresponding to the conditions listed above.

## DOAC blood concentration

In addition to the study endpoints, we will perform an auxiliary analysis that assess the correlation between DOAC concentration and medication adherence as well as treatment outcomes. For all patients enrolled in the trial, DOAC concentration will be measured at the three-month and six-month physician follow-up visits. The blood sample will be collected through venous puncturing in a K2EDTA (BD Vacutainer®) tube containing citrate. The time of sampling is trough, defined as at least 10 hours from last dose of dabigatran or apixaban, or at least 22 hours from the last dose of rivaroxaban or edoxaban. The blood sample will be centrifuged with a standard procedure and stored at -80 degrees Celsius. The DOAC concentration will be measured by using the ultra-high-performance liquid chromatography with tandem mass spectrometry (UHPLC-MS/MS). The method has been validated and published before.[21]

The instrument that will be used is an Agilent 1290 UHPLC system coupled with an Agilent 6460 triple quadrupole mass spectrometer (Agilent Technologies, Santa Clara, CA). A Kinetex reversed-phase

core-shell C18 column (2.1 × 50 mm, 2.6 μm, 100 Å, Phenomenex, Torrance, CA, USA) will be used for the separation. The mobile phase will consist of 0.1% formic acid in water (solvent A) and 0.1% formic acid in ACN (solvent B). The flow rate will be 0.35 mL $min^{-1}$. The gradient profile will start with 1% B for 0.5 min, then change to 15% B in 0.1 min and remain at 15% B for 0.9 min, and then increase to 100% B in 0.6 min and is maintained for 1.4 min. Finally, the column will be re-equilibrated to 1% B for 1.5 min until the next injection. The temperature of the sample reservoir will be maintained at 4°C, and the column oven will be set at 40°C. The injection volume will be 3 μL. The JetStream electrospray ionizer will be employed as the ion source. The MS parameters will be set as follows: a 350°C drying gas temperature, a 10 L/min drying gas flow rate, a 45 psi nebulizer pressure, a 350°C sheath gas temperature, an 11 L/min sheath gas flow rate, a 3500 V capillary voltage, and a 500 V nozzle voltage. MS acquisition will be executed in multiple reaction monitoring mode and the mass transitions were 472.2→289 and 472.2→144 for dabigatran, and 478.2→295.1 for the isotopic internal standard [$^{13}C_6$]-Dabigatran; 460.2→443.1 and 460.2→199 for apixaban, and 464.2→203.1 for the isotopic internal standard [$^{13}C$, $d_3$]-apixaban; 436.1→144.9 and 436.1→72.9 for rivaroxaban, and 442.1→144.9 for the isotopic internal standard [$^{13}C_6$]-rivaroxaban; 460.2→443.1 and 460.2→199 for Edoxaban, and 554.1→372.1 and 554.1→153 for the isotopic internal standard [$d_6$]-Edoxaban. We will collaborate with the NTU Medical School Drug Research Center for blood sample analysis.[22]

**Statistical Analysis**

In Aim 1, we will first report and compare patients' baseline characteristics by arms with descriptive statistics. Continuous variables will be compared by t-tests, and dichotomous or categorical variables will be compared by chi-square tests. The significance level will be set at 0.05 with a two-sided approach. We will use the intention-to-treat approach to analyze data from all randomized patients. For the primary endpoint, we will use both t-tests and linear regressions to evaluate the between-group differences and the magnitude of change in ARMS scores between the two arms, respectively. For the secondary endpoint, we will use the time-to-event approach to compare the hazard of event development between the two arms.

In Aim 2, to understand the reasons of non-adherence to medication, we will begin with a report on the frequency and percentage of patients' responses to the items related to medication taking in the ARMS. The summary score of the eight items measuring medication adherence in the ARMS will be correlated with the PDC measured in the NHI claims using Spearman correlation. Likewise, we will correlate the summary score of the four items measuring refill adherence in the ARMS to the refill records in the NIH claims data using Spearman correlation.

In Aim 3, to understand the correlation between the DOAC blood concentration and medication adherence, we will dichotomize patients into high and low adherence groups based on the median ARMS score. Subsequently, we will compare the proportion of patients with blood concentrations within the therapeutic range between the two adherence levels by chi-square tests. Similarly, to understand the correlation between the DOAC concentration and treatment outcomes, we will first categorized patients into three groups based on their DOAC concentration: above the therapeutic range, within the therapeutic range, and below the therapeutic range. We will then compare the proportion of patients experiencing an event among those three groups by chi-square tests.

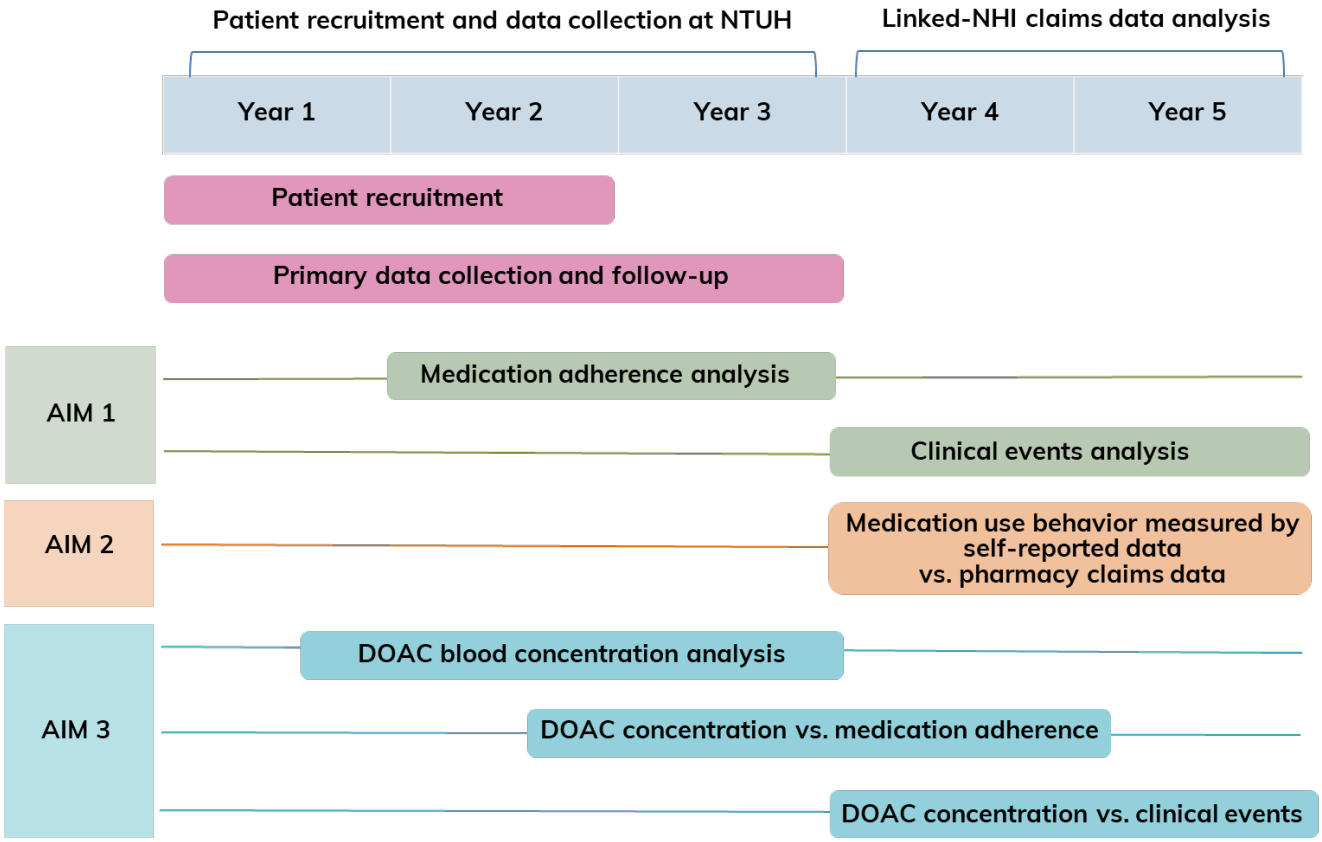
To better understand the potential heterogeneity in the effect of patient education across different groups, we will first analyze the entire study population based on the randomization results to assess the overall effectiveness of pharmacist-led education. Next, we will conduct stratified analyses by the level of prevention (primary or secondary) to evaluate whether the effectiveness differs between these two subgroups.

**Study Timeline**

The overall timeline proposed for this study is five years. We plan to recruit eligible patients in the first two years. All patients will be followed for six months, and patient follow-up will occur from year one to year three. Once we complete the follow-up and data collection, we will analyze data on DAOC

use behavior, including medication adherence and refill adherence in year two and three. Analysis on DOAC blood concentration is expected to occur between year two and year four, depending on the capacity of the NTU Medical School Drug Research Center. Finally, in year four and five, we will acquire the NHI claims data for clinical event follow-up. As the Health and Welfare Data Science Center typically releases the NHI claims data from the previous year in the second quarter of the current year, we will need to wait until year four to get the complete patient follow-up data. We therefore plan to analyze patients' one-year follow-up outcomes in year four and the two-year follow-up outcomes in year five. Figure 4 below presents the study timeline by aims.

**Figure 4. Graphical illustration of the study timeline by study aims**




NTUH: National Taiwan University Hospital; NHI: National Health Insurance; DOAC: direct oral anticoagulant.

## ANTICIPATED RESULTS

Findings from this trial will enhance our understanding about the impact of pharmacist-led intervention on patients' adherence and treatment outcome. We expect that the intervention will improve patients' medication adherence and treatment outcomes. While our study focuses on DOAC users, the results should be applicable to other medication treatments for chronic conditions, as the primary goal of most treatments for chronic conditions is to prevent future events. Moreover, the frequency of medication administration for DOACs is comparable to that of medications used to treat other common chronic conditions. For instance, DOACs are typically administered once or twice daily, a regimen similar to that of common treatments for hypertension, diabetes, and hyperlipidemia. The simplicity of our intervention increases its relevance to routine practice. Our intervention, which consists of one-time patient education and two follow-up visits spaced three months apart, features a straightforward design that can be readily adapted to other therapeutic areas.

In Aim 2, we expect to find good refill adherence but suboptimal medication adherence among patients taking DOACs. While we anticipate that most patients in Taiwan will refill their prescriptions due to the low out-of-pocket costs and easy access to healthcare services, there may still be instances where patients do not adhere to their prescribed medication regimen after obtaining their refills. Importantly, this pattern of medication non-adherence cannot be detected by secondary data sources such

as EMRs or claims data. Our results will provide further insight on the reasons behind non-adherence. Understanding the reasons for non-adherence will enable pharmacists and other healthcare providers to customize patient education, improving patient communication. For example, through this project, we will be able to understand whether patients miss doses due to forgetfulness or a perceived control of their condition, leading to a reduction in medication frequency. The findings from Aim 2 can also serve as valuable input for shaping the structure and content of future patient education initiatives.

In Aim 3, we expect to observe a significant correlation between DOAC blood concentration and medication adherence. A higher proportion of patients with good adherence are anticipated to have a DOAC blood concentration falling within the expected range. We expect to find a low-to moderate correlation between DOAC blood concentration and treatment outcomes because of two reasons. First, the incidence rate of thromboembolism and major bleeding during DOAC therapy reported in clinical trials are low (approximately 1.7% and 3.0%, respectively). The rate will be even lower in patients using DOAC for stroke prevention. Second, DOAC concentration may not completely reflects the medication adherence as DOACs are medications that have rapid onset. Therefore, we design repeated DOAC concentration measurement in this study. Despite of these concerns, the association between DOAC concentration and clinical outcomes has been well-established.[23-25] Understanding this correlation will help us to understand the role of DOAC level on measurement of drug adherence, and further enhance the DOAC management.

Finally, students involving in this project will receive comprehensive training on study designs, patient education, data collection, and gain hands-on experience on data analysis. This project will also create chances for cooperation between the academic and the clinical settings, which will allow students to have multi-disciplinary training. Students and all the personnel in our research team will have the chance to attend international conference to present our study findings. We also expect to have peer-reviewed journal publications from this project.

**HUMAN SUBJECTS**

In this study, we will recruit patients aged ≥18 years old, diagnosed with AF, and are expect to receive DOAC for at least three months for stroke prevention. We will exclude patients who are illiterate, have cognitive impairment, receive off-label DOAC regimens, or have a history of thromboembolic events. Eligible patients for this study will receive clear explanations about the intervention, including patient education, surveys regarding medication use behavior, and blood draws for DOAC concentration. Patients will also be informed about the two additional ACC follow-up visits, as well as the utilization of their EMRs and the NHI claims data for baseline assessment and follow-up, respectively. Since the EMRs contain all the required information about the patients, no additional information will be collected from the patients, except the medication taking behavior. Only patients who signed the informed consent form will be included in the study, and patients will be informed that they can withdraw from the study at any time after the recruitment without any reasons.

All participants will receive standard care regardless of their intervention assignment. This study will not infringe patients' right of seeking medical care or treatment, and only minimal risk will be involved. After each ACC visit, the participants will receive a gift card valued at $200.

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