

**Pharmacist Management of Paxlovid eVisits:
A Randomized Clinical Trial**

Study Protocol and Statistical Analysis Plan

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Abstract

Importance. Enhancing the management of messages from patients and providing virtual options for urgent care are top priorities for The Permanente Medical Group (TPMG) and Kaiser Foundation Hospitals/Health Plan (KFH/P).

Objective. To compare pharmacist management of e-visit requests for Paxlovid for COVID-19 with management by adult and family medicine physician pools regarding costs, time, clinical outcomes, and patient and clinician satisfaction.

Design, setting, and participants. This cluster randomized clinical trial will include adults from 17 medical facilities of Kaiser Permanente Northern California who make Paxlovid e-visits on weekdays from October 9 to December 11, 2023.

Intervention. In the intervention group, a regional team of pharmacists will manage Paxlovid e-visits following a standard protocol; in the comparison group, adult and family medicine physicians (AFMs) will manage these visits according to medical center-based protocols.

Main Outcomes and Measures. The primary outcome is whether a patient with one or more common drug-drug interactions received counseling for any drug-drug interaction. Secondary outcomes are the hours from the e-visit request to the prescription among patients who receive one and the clinician time and cost per visit managed.

Potential Results. We will test the hypotheses that Pharmacist Care compared with AFM Pool Care will have higher quality of care and lower costs based on the receipt of counseling for common drug-drug interactions, faster time to prescriptions, and lower clinician time and cost per visit managed.

Potential Conclusions and Relevance. If pharmacist management has better or similar outcomes compared with AFM pool management, this will provide support to continue this practice for Paxlovid e-visits and to evaluate possible expansion of pharmacist management for similar clinical situations.

1. Specific Aims and Hypotheses

Enhancing message management and virtual urgent care options for patients are among TPMG and KFH's top priorities. As team-based inbox management is further developed, evaluating its clinical effectiveness and outcomes in terms of patient care experience and costs will provide valuable information for operational planning. In addition, sharing what we learn with other health care systems through talks and publications will help highlight TPMG's reputation as a group that innovates to support clinicians while increasing patient access through virtual care.

This study will compare the clinical outcomes and costs of two alternative modes of management of patient requests for Paxlovid sent via e-visits: management by a regional team of pharmacists, vs. management by medical center-based pools of adult and family medicine physicians (AFMs) doing desktop medicine. We will conduct a cluster randomized trial in 17 facilities in Kaiser Permanente Northern California to compare Pharmacist Care with AFM Pool Care for patients making Paxlovid e-visits with regard to:

Aim 1. Quality of care

Example hypothesis: Patients with common potential DDIs will be more likely to receive relevant counseling in the Pharmacist Care group than the AFM Pool Care group.

Aim 2. Clinician time and costs

Example hypothesis: Pharmacist Care will have lower costs of clinician time per Paxlovid e-visit managed than AFM Pool Care.

Aim 3. Exploratory outcomes

Example hypothesis: Patients in the Pharmacist Care will report comparable satisfaction with the process compared with the AFM Pool Care group.

2. Background and Significance

Physicians experience substantial stress associated with managing their electronic health record (EHR) inboxes.¹⁻³ Much of physicians' time in the EHR inbox involves answering messages from patients.⁴ The volume of messages is a key driver of stress and attention switching.^{1,5}

Assisting physicians with message management is a top priority for The Permanente Medical Group (TPMG). A variety of approaches are possible. Team-based approaches that involve pharmacists and other clinical staff have been recommended, and anecdotal report suggests they have been successful in some settings.⁶ However, scant systematic evidence exists on whether such approaches are effective in terms of timeliness or quality of care, or in actually saving physicians' time.

This study will address this important gap in evidence via a cluster randomized trial comparing pharmacist management of patient e-visit requests for nirmatrelvir-ritonavir (Paxlovid) with management by pools of adult and family medicine (AFM) physicians. The latter was the default approach by most Kaiser Permanente Northern California (KPNC) medical centers before 2023. The findings will have broad implications for regional care delivery planning, as TPMG and KFH consider whether and how to have pharmacists and other clinical team members participate in message management. This study will inform operational decisions and practice for both Kaiser Permanente and other health care systems in the U.S. and beyond.

3. Innovation

Pharmacist management of secure messages from patients is innovative in not having been adopted or evaluated at large scale. Preliminary anecdotal and unpublished information from within TPMG suggests that pharmacists' scope of practice is well-suited to message management for many specific conditions based on treatment algorithms. At our KP San Francisco medical center, pharmacists have been able to take charge of messages for a range of issues, including refill authorization requests and requests to manage chronic conditions (hypertension, osteoporosis, attention deficit disorder, gout) and time-limited conditions (sexually transmitted infections, latent tuberculosis, opioid tapering, and assessment of Paxlovid eligibility).

E-visit management is another innovative aspect of this study. Kaiser Permanente Northern California (KPNC) is ahead of most other systems nationally in its implementation of e-visits.

Enhancing the accessibility of urgent care through digital and other means is a key priority for TPMG as well as KP generally.

4. Approach

4.1. Design, setting, and participants.

This cluster randomized clinical trial will assign patient requests for Paxlovid made via e-visits to either Pharmacist Care or AFM Pool Care, which consists of management by medical center-based pools of AFMs in adult and family medicine (AFM). The unit of randomization is the KPNC facility. KPNC is an integrated health care system with 4.6 million members served by more than 9,500 physicians and 87,000 employees in 15 service areas. It has a mature EHR (EPIC/HealthConnect, adopted circa 2008) and encourages members to use a wide array of options for outpatient care, including secure messages to physicians via the EHR portal, e-visits, video, telephone, and in-person office visits.

The target population is adults 18 years and older in facilities within participating KPNC service areas who submit requests for Paxlovid on weekdays during the study period using the e-visit protocol accessible via the electronic portal kp.org. Messages that are handled from 8:00 am to 4:30 pm, Monday through Friday will be included. The study period will run from October 9 to December 11, 2023. Pharmacist Care will not be available for Paxlovid e-visits that need to be reviewed on weekends or holidays. These are managed by virtualist physicians in the regional call center and will be excluded from this study.

Of KPNC's 15 service areas, 4 have not implemented pharmacist management in any facility. These service areas and their facilities are eligible for this study; others must be excluded. The eligible service areas are SCL, SJO, SRF, and SSC. These service areas contain 17 facilities; each facility will be treated as a cluster in the random assignment process.

4.2. Intervention.

All procedures will be conducted as part of standard of care. In the Pharmacist Care group, each e-visit message requesting Paxlovid will be assigned to a pharmacist on the regional team. Pharmacists will review requests using a standard protocol. They will call patients via telephone to elicit additional information where needed, file Paxlovid prescriptions when appropriate, and arrange home delivery when requested.

The protocol for pharmacists has a list of common potential drug-drug interactions and provides guidance for how these should be handled. Drug-drug interactions are documented by pharmacists using a smartphrase in Epic, the electronic health record (EHR). Some DDIs may lead to changes in medications while a patient is taking Paxlovid.

In the AFM Pool Care group, each e-visit message requesting Paxlovid will be assigned to a pool of AFM physicians based at the medical centers in a given service area. Physicians will review requests using the existing standard regional protocol (as well as any existing medical center-level protocols). The regional Paxlovid E-visit User Guide illustrates how to use SmartSets to document the plan and respond to patients with the outcome (eligible, not eligible, or further discussion needed). Following this protocol, physicians call patients via telephone to elicit additional information where needed, file Paxlovid prescriptions when appropriate, and arrange home delivery when requested.

4.3. Randomization. In each of the participating service areas, facilities have been assigned at random to either the Pharmacist Care or AFM Pool Care group. We used covariate-constrained randomization, a method to prevent imbalances on important variables that may be associated with the outcomes.⁷ We conducted preliminary analyses to characterize facilities with regard to population size, socioeconomic status (using the Neighborhood Deprivation Index), race, ethnicity, and COVID-19 incidence in the service area since the start of the pandemic. We have chosen these variables for use in the restricted randomization given the expected association with study outcomes, along with the expected level of between facility variability which would increase the likelihood of between-arm imbalance. We also stratify randomization on service area for within-area balance on number of facilities assigned to the Pharmacist Care and AFM Care groups.

Using these variables, we enumerated all possible outcomes of randomization and eliminated all allocations of the facilities to the two groups that do not meet specified between-group balance criteria. Standard diagnostics were applied in selecting the covariate balance criteria, ensuring no threats to the validity of the study design, including extreme reductions in total possible allocations for the trial, and instances of cluster pairs never/rarely or always/often randomized to the same arm. An allocation of facilities to the two arms for implementation was randomly selected from the set of allocations that meet the final covariate balance criteria.

The balance criteria were: maximum 5% between arm difference in total membership, 30% difference in total Black, 20% for each of White, Asian and Hispanic race/ethnic groups, 25% difference in mean NDI, and 15% difference in mean COVID-19 incidence. We are applying no between arm balance criteria within strata/service area.

The selected randomization scheme leads to good balance between the intervention and comparison groups, with 4.8% difference in total membership (~565K vs ~513K), 11.7% for Black (23K vs 29K), 2.2% for White (183K vs 175K), 8.7% Asian (150K vs 126K), 7.8% Hispanic (127K vs 109K), 12.2% difference in mean NDI (-.49 vs -.44), and 2.7% difference in mean COVID-19 incidence (.23 vs .22).

4.4. Main outcomes and measures

4.4.1. Outcomes

The primary outcome will be measured only among patients who have common potential drug-drug interactions (DDIs) based on a pre-specified list of medications. The outcome will be whether the patient received counseling for any valid potential DDI. For patients with more than one DDI, the outcome will be counted as present if they received counseling for any of their potential DDIs.

Secondary outcomes will be:

- a. % of all patients who were prescribed Paxlovid (based on orders)
- b. Hours from the e-visit request to the prescription order being placed, among patients who were prescribed Paxlovid
- c. Clinician minutes per message handled. This will be analyzed using EPIC access log data. We will link each e-visit for Paxlovid with the relevant secure messages and/or

telephone encounters, including follow-ups that occurred before the initial request was resolved. Clinicians include pharmacists and physicians.

- d. Estimated personnel cost per Paxlovid message handled. The estimated cost per message handled will be calculated by multiplying the number of minutes spent per message by the standard wage rate for a pharmacist or AFM in Northern California.
- e. Patient satisfaction with care

Exploratory outcomes will be:

- a. Number of Paxlovid e-visits handled by the regional pharmacy team, per week
- b. % of messages fully handled by the initial clinician (pharmacist or AFM) (based on review of visits)
- c. % of cases handled by pharmacists that required a physician consultation (based on review of visits)
- d. Pharmacist satisfaction with the process of care
[Note: Deleted "AFM satisfaction" as a measure because there was not a logical group of AFMs to survey, nor logical questions to ask them.]
- e. % of all patients who obtained Paxlovid (based on fills)
- f. Days from request to receipt of medication among patients prescribed Paxlovid
- g. % of patients with common potential DDIs who were prescribed Paxlovid
- h. If feasible based on ICD-9 codes: Incidence of drug reactions due to Paxlovid DDIs within 10 days after a Paxlovid prescription

4.4.2. Predictors and covariates

The primary predictor is study group, i.e. Pharmacist Care or AFM Pool Care. Covariates are other variables that could potentially mediate, moderate, or confound the association between the primary predictor and the outcomes. In this study, covariates include patient age, sex, race, ethnicity, language spoken, and comorbidities, as well as the patient's neighborhood-level SES.

4.5. Data collection.

The primary outcome will be measured only among patients who have common potential drug-drug interactions (DDIs) based on a pre-specified list of medications. The outcome will be whether or not they received relevant counseling for any of their DDIs. Eligible patients in both groups will be selected using computerized pharmacy codes generated based on the protocol used by the regional pharmacy team. The computerized pharmacy codes will be used to identify patients with any of these potential DDIs in a consistent way in the Pharmacist Care and AFM Pool Care groups.

Research assistants blinded to group assignment will review text extracts from the EHR using a structured protocol to identify whether there is documentation that the patient received counseling regarding a DDI. With each study group, a random sample of eligible patients will be identified; the sample will be stratified by facility to yield a representative sample. Masking of group assignment will be conducted by one research assistant prior to review by a different

research assistant. A patient with any potential DDI will be counted as having received relevant counseling if any counseling (for any potential DDI) was documented in the text extra prior to or coincident with a Paxlovid prescription, or in the absence of a Paxlovid prescription, occurring within 2 days after the e-visit.

For the secondary outcomes, we will use data available from KPNC computerized sources, including HealthConnect (HC, aka EPIC) EHR data (from Clarity) and EPIC access logs. EHR data will be used to identify all e-visits for Paxlovid during the study period. For each patient who made an e-visit, the EPIC access log data for the subsequent 5-day period will be analyzed to identify how many minutes of pharmacist or physician time were associated with that request.

For the exploratory outcomes, patient care experience will be evaluated by surveying a sample of patients selected at random in the service areas in the Pharmacist Care and AFM Pool Care groups. We have designed a short survey that takes no more than 5 to 10 minutes to complete. The survey will be fielded by email, mail, and telephone. Due to the fact that we are asking about a specific care experience and patients' recall fades quickly after 2 weeks, we will field the survey using all 3 modes in a relatively efficient sequence. A letter containing a description of the study, language regarding informed consent and confidentiality, and the survey will be sent by mail on day 11 after the e-visit, and an email with a link to the online version will be sent on day 14. Telephone administration will be attempted (up to 4 attempts total) starting on day 17 for those who have not replied to the paper or online survey. A small gift to thank patients for considering participation will be included in the mailing. Responses will be treated as confidential and data will be aggregated, with no individual identifiers associated with data presented in reports.

Patient-reported outcomes will be reported on a 5-point scale and will include:

- a. Satisfaction with the overall quality of care
- b. Satisfaction with the timeliness of care
- c. Confidence in the care provided

Clinician satisfaction with the process of care will be evaluated by surveying all pharmacists on the regional team providing Pharmacist Care, plus the AFM site leads for Paxlovid e-visits in the service areas participating in the study. Because the AFMs in each service area cross-cover the Paxlovid e-visit requests from all facilities in that service area, it will not be possible to survey front-line AFMs in the two groups separately, and it would not be productive to ask the AFMs about their experience with Pharmacist Care because they would typically only have direct experience with Pharmacist Care if a problem arose that required their attention.

The pharmacist and physician surveys have been designed to require no more than 3 to 5 minutes to complete. These surveys will be fielded via Outlook email using a Teams form, as well as on paper via interoffice mail. A small gift to thank pharmacists and physicians for considering participation will be included in the mailing. Responses will be treated as confidential and data will be aggregated, with no individual identifiers associated with data presented in reports.

Data collected from both pharmacists AFMs and will include:

- a. Satisfaction with the process of care (on a 5-point scale)
- b. Suggestions for improving the care process (open-ended)

4.6. Statistical analysis plan.

During the survey and visit review components of this study, it became clear that more patients than projected had received pharmacist care. A preliminary analysis conducted on 12/18/2024, prior to evaluating any outcomes, found that the facility assigned to each e-visit usually did *not* match the home facility of the patient who initiated the e-visit. This was most likely due to an operational workflow (which is still being elucidated) that was unanticipated at the time this study was designed and facilities were assigned at random to the Pharmacist Care vs. Physician Care groups. Due to the fact that the patient's "home" facility became imbalanced, we will include this as a covariate in the primary analysis (see below).

The primary analysis will group each patient based on which type of clinician (pharmacist or physician) first accessed the eVisit. This is similar to a per-protocol analysis. A patient whose eVisit was first accessed by a pharmacist will be counted in the pharmacist group, even if the eVisit was referred to a physician. A patient whose eVisit was first accessed by a physician will be included in the physician group, even if the eVisit was referred to a pharmacist. We select this approach as the primary analysis because it best reflects what patients experience in real-life care delivery, which this study is intended to evaluate.

A secondary analysis will treat each patient as part of the group to which they were assigned based on the facility listed on the e-visit worklist (intention-to-treat). However, this approach may be worse at reflecting the actual patient experience because dozens of pharmacists and physicians were involved in executing the randomization assignments. It is possible that some patients will have received a different mode of care from the group to which they were assigned.

The primary outcome is binary, i.e., whether or not a patient received counseling for a DDI. This will be compared between study groups using mixed effects logistic regression providing point and interval estimates of outcome odds ratios associated with study group. This analysis technique accounts for the within-facility correlation among patients to obtain valid estimates of treatment effects and associated standard errors. The pre-specified set of covariates for inclusion in regression models include: study group and covariates used in the randomization procedure (i.e. patient socioeconomic status (using the Neighborhood Deprivation Index), patient race/ethnicity, and service area level COVID-19 incidence). Study group and other covariates will be treated as fixed effects and the patient's home facility and e-visit facility will be handled as random effects.

In addition, exploratory/sensitivity analyses will examine the impact of including additional covariates in our estimation of treatment effect, with focus on variables with chance imbalance in distributions by treatment group, as determined in preliminary analyses. Analyses resulting in an appreciable change in the estimate of treatment differences or increased precision of the treatment effect will be noted.

For the secondary outcomes, we will compare the estimated cost per Paxlovid message, the minutes spent per message, and the hours from e-visit to prescription order between the Pharmacist Care and AFM Pool Care groups using linear mixed regression models, providing point and interval estimates of between-group differences in mean outcomes. If cost or minutes have a skewed distribution, log transformation will be used. Analyses of other secondary outcomes with that are continuous will be similar. The approach to inclusion of covariates and sensitivity/exploratory analyses is as described for Aim 1.

Patient satisfaction and other care experience scores will be compared between the study groups using linear mixed effects regression with log transformation if needed for skewed data, with analyses paralleling that described for the other secondary outcomes.

For all aims, secondary analyses will assess variation in the estimates of treatment effect by age, race/ethnicity/language group, and comorbidity score group (high, medium, low) via stratification by level of the potential effect modifier. These stratified analyses will inform the fitting of regression models with appropriate cross-product terms between the potential effect modifier and study group indicator variable, allowing for a more formal assessment of heterogeneity in treatment effect.

A service area or facility may drop out before completion of the study if they were assigned to AFM Pool Care but add local pharmacist management, thus diverging from their assigned group. Paxlovid e-visits from such a service area or facility will be censored as of the dropout date (the date that local pharmacist management began).

Tests of significance will be two-tailed with an alpha of .05. No Bonferroni or other formal correction for multiple comparisons will be used, but results will be interpreted with the multiple testing issue in mind.

4.8. Sample size and power. To estimate the available sample, we extrapolated from April 2023. This was a month when COVID-19 incidence was low to medium; 4900 e-visits for Paxlovid were made across the 15 KPNC service areas. Based on this, an average of 1089 e-visits occur per week during low to medium COVID-19 incidence periods. However, e-visits that need to be answered on weekend days will not be eligible for pharmacist management; all of these will be excluded from the study. If 5 out of 7 e-visits occur on weekdays, an estimated 778 e-visits occur on weekdays during times of low to medium COVID-19 incidence.

This study will include 17 facilities that serve 872,200 adult members, or 25% of the 3.55 million adult members in the region. Each week, the estimated number of e-visits eligible for study is 25% of 778, or 195. Assuming an 8-week evaluation period, the estimated sample size is 1,560, or 92 patients in each of the 17 clusters.

Given the group-randomization study design, calculation of sample sizes and minimum detectable treatment effects must account for the expected intraclass correlation (ICC) of observations within facilities. The ICCs in outcomes of interest are expected to be quite small, and therefore we present minimum detectable effects for an expected ICC of .01.

For Aim 1, the primary outcome is the % of patients with common potential DDIs who received counseling. We conservatively estimate that 70% of patients in the Pharmacist Care group will have received DDI counseling. A clinically meaningful difference between the two groups would be a relative risk (RR) of 0.8, which corresponds to a small effect size. To attain 80% power to identify such an effect with a two-tailed alpha of 0.05 and an ICC of .01, we need a sample size of 250 in each group and will plan our review of text extracts from the EHR accordingly.

For Aim 2, the example hypothesis is that the cost of management per e-visit for Paxlovid will be lower in the Pharmacist Care group than in the AFM Pool Care group. Given a two-tailed alpha of .05, the sample size of this study has 80% power to identify an effect size of 0.20 standard deviation units, which is a relatively small effect size. In other words, this study will have good power to find a statistically significant difference between the Pharmacist Care and AFM Pool Care groups even if the effect is relatively small.

For the patient survey in Aim 3, the sample size is selected to balance power and feasibility. We aim to collect completed surveys from 200 patients in each of the two study groups. We

estimate a response rate of 60%. To obtain 200 completed surveys in each group, we estimate needing to attempt surveys with 333 patients in each group. The completed sample size of 200 in each group will give us good power to identify relatively small differences in satisfaction scores, which are measured on a continuous scale. We will be able to detect effect sizes of .31 relative to a standard deviation of 1.

The purpose of the pharmacist and AFM surveys is process assessment and performance improvement. These surveys will focus on qualitative, open-ended responses; thus, sample size and power are not estimated here. We will survey all pharmacists on the regional team providing Paxlovid e-visits (estimated n=10). We also will survey the AFMs who are Paxlovid e-visit site leads (estimated n=12).

4.9 Timeline

Date	Operational team	Research team
Sep 25	Pilot care delivery to the service areas to receive Pharmacist Care; run-in period	Not included in study
Oct 9	Continue care delivery at steady state	Start of study period <ul style="list-style-type: none"> - Conduct review of text extracts from the EHR (random sample throughout period) - Conduct patient surveys (random sample throughout period) - Conduct pharmacist and AFM surveys (mid-Nov. to early Dec.)
Dec 11	End study – pharmacists cover all service areas	End of study period
Dec 11 – Jan 12		Analyze computerized data of outcomes for Aims 1 and 2 Complete data collection with clinicians and patients
Jan 12 – Feb 2		Finish cleaning and analysis of data from clinicians and patients
Feb 2 –		Create reports for internal use Share findings with other TPMG and KFH leaders Draft manuscript for journal submission

4. Projected Impact

This study's findings quality of care, cost, and patient and clinician satisfaction will inform decisions about how to deploy pharmacist effort for KPNC. The study leaders include regional leaders for Virtual Medicine and Pharmacy who are well-positioned to make implementation decisions based on the results we generate.

5. Deliverables and Dissemination Plan

Our deliverables and dissemination plan have two purposes: To provide information for operational decisions by TPMG and KFH, and to establish our reputation as leaders in Desktop Medicine and Pharmacy Services through publication. Specific deliverables and plans include:

- The PI will prepare a presentation prior to study initiation to support conversations with leaders of service areas that will be included.
- Soon after the analysis of computerized data is completed, we will create an internal report for Drs. Lee and DeLaunay to share via presentation to the appropriate chiefs and other operational leadership groups.
- The analysis of clinician and patient data will be completed after this, and we will update the internal report to support a follow-up communication.
- We will write a manuscript for submission to a peer-reviewed journal to share our findings with health care leaders in the U.S. and beyond.

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