Implementation of an anticoagulation practice guideline for COVID 19 via a clinical decision support system in a large academic health system and its RE-AIM evaluation

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Submitted to: JMIR Medical Informatics
on: May 27, 2021

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Abstract

Background: Studies evaluating strategies for the rapid development, implementation and evaluation of clinical decision support(CDS) systems supporting guidelines for diseases with poor knowledge base, such as COVID-19, are limited.

Objective: We developed an anticoagulation clinical practice consensus guideline(CPG) for COVID-19 delivered and scaled via CDS across a 12-hospital Midwest healthcare system. This study represents a pre-planned 6-month post-implementation evaluation guided by the RE-AIM framework.

Methods: Implementation outcomes evaluated include reach, adoption, implementation, and maintenance. To evaluate effectiveness, the association of CPG adherence was assessed using multivariable logistic regression. The primary effectiveness endpoint was the need for ICU admission within 48 hours of hospital admission.

Results: 2,503 patients were included in this study. CDS reach approached 95% during implementation. Adherence achieved a peak of 72% during implementation. Variation was noted in adoption across sites and nursing units. Adoption was best at COVID-19 cohorted hospitals(74-82%) and lowest at academic settings(47-55%). CPG delivery via CDS was associated with improved adherence (OR 1.43, 95%CI 1.2-1.7, p<0.001). Adherence with the anticoagulation CPG was associated with a significant reduction in the need for ICU within 48 hours (OR 0.39, 95%CI 0.30–0.51, p<0.001).

Conclusions: Our institutional experience demonstrated that adherence with institutional CPG delivered via CDS resulted in improved clinical outcomes for patients with COVID-19. CDS are an effective means to rapidly scale a CPG across a heterogeneous healthcare system. Further research is needed to investigate factors associated with adherence at low and high adopting sites and nursing units.

(JMIR Preprints 27/05/2021:30743)
DOI: https://doi.org/10.2196/preprints.30743

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Implementation of an anticoagulation practice guideline for COVID 19 via a clinical decision support system in a large academic health system and its RE-AIM evaluation

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Brief Title: COVID-19 Anticoagulation Clinical Decision Support

Word Count: 3936 of 4000 words (word count was increased to adequately response to reviewer comments)

DATA AVAILABILITY

The data underlying this article were provided by M Health Fairview (Minneapolis, MN, USA) by permission from the M Health Fairview Research and IT. Data will be shared on request to the corresponding author with permission of M Health Fairview.

ABSTRACT

Background: Studies evaluating strategies for the rapid development, implementation and evaluation of clinical decision support(CDS) systems supporting guidelines for diseases with poor knowledge base, such as COVID-19, are limited.

Objective: We developed an anticoagulation clinical practice consensus guideline(CPG) for COVID-19 delivered and scaled via CDS across a 12-hospital Midwest healthcare system. This study represents a pre-planned 6-month post-implementation evaluation guided by the RE-AIM framework.

Materials and Methods: Implementation outcomes evaluated include reach, adoption, implementation, and maintenance. To evaluate effectiveness, the association of CPG adherence on hospital admission was assessed via multivariable logistic regression and nearest neighbor propensity

score matching. A time-to-event analysis was conducted. Sensitivity analyses were also conducted to evaluate the competing risk of death prior to ICU admission. Models were risk adjusted to account for age, gender, race/ethnicity, non-English speaking status, area deprivation index, month of admission, remdesivir, tocilizumab, steroid treatments, body mass index, Elixhauser Comorbidity Index, Oxygen Saturation/FiO2 ratio, systolic blood pressure, respiratory rate, treating hospital, and source of admission. A preplanned subgroup analysis was also conducted in patients that had lab values: D-dimer, C-reactive Protein, Creatinine, and Absolute neutrophil-absolute lymphocyte ratio present. The primary effectiveness endpoint was the need for ICU admission within 48 hours of hospital admission.

Results: 2,503 patients were included in this study. CDS reach approached 95% during implementation. Adherence achieved a peak of 72% during implementation. Variation was noted in adoption across sites and nursing units. Adoption was best at COVID-19 cohorted hospitals(74-82%) and lowest at academic settings(47-55%). CPG delivery via CDS was associated with improved adherence (OR 1.43, 95%CI 1.2-1.7, p<0.001). Adherence with the anticoagulation CPG was associated with a significant reduction in the need for ICU within 48 hours (OR 0.39, 95%CI 0.30–0.51, p<0.001) on multivariable logistic regression analysis. Similar findings were noted following 1:1 propensity score matching for patients that received adherence vs non-adherent care (21.5% vs 34.3% incidence of ICU admission within 48 hours, log-rank test p < 0.001).

Discussion: Our institutional experience demonstrated that adherence with institutional CPG delivered via CDS resulted in improved clinical outcomes for patients with COVID-19.

Conclusion: CDS are an effective means to rapidly scale a CPG across a heterogeneous healthcare system. Further research is needed to investigate factors associated with adherence at low and high adopting sites and nursing units.

KEYWORDS:

COVID-19, anticoagulation, clinical practice guideline, evidence-based practice, clinical decision support, implementation science, RE-AIM

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Introduction

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has infected millions worldwide. This disease has shown many unique attributes including a hypercoagulable profile.[1-4] COVID-19 associated coagulopathy (CAC) results in widespread macro and microvascular thrombosis contributing to multisystem organ failure and thus contributes to significant mortality and morbidity.[5] Observational and recent randomized controlled studies in COVID-19 and other viral pneumonias suggest that routine anticoagulation is associated with improved clinical outcomes for hospitalized patients.[6-10] Given this, our healthcare system developed a clinical practice consensus guideline (CPG) delivered as a clinical decision support (CDS) system to facilitate guideline-driven anticoagulation for COVID-19 patients.

CDS technology solutions offer a mechanism that in support of the learning health system (LHS) facilitate long-term process and quality measure improvement.[11,12] CDS systems leverage the electronic health record (EHR) to deliver process-specific information to health care teams, aiding clinical decision-making. When designed well and implemented effectively, CDS systems have been shown to improve adherence with evidence-based practice and in some cases improve clinical outcomes.[11-13] Unfortunately, best practices for successful implementation and scaling of CDS are still unknown.[14] Furthermore, very little is known about developing, implementing, and scaling CDS interventions during a pandemic with rapidly changing evidence-base and strained clinical resources across diverse sites.

On April 9, 2020, our institution developed and disseminated a three-tiered clinical-practice guideline (CPG) for anticoagulation in COVID-19 in collaboration with national experts

(Supplemental Figure 1). Given rapid evolution of evidence, this CPG has evolved over time to reflect best practice based on the available evidence at the time.[4,7] To maximize dissemination and reach of the CPG, a clinical decision support (CDS) solution was developed to deliver the CPG including both passive and interruptive alerts, piloted at a single site on May 14, 2020, and successfully scaled across a 12-hospital Midwest healthcare system on May 24, 2020. An interim reach, adoption, and effectiveness evaluation occurred 3 months following implementation on August 19, 2020 (Figure 1).

This study represents a pre-planned 6-month implementation evaluation guided by the RE-AIM framework[15] of the anticoagulation CPG CDS system for patients admitted with COVID-19 between March 4, 2020 – December 4, 2020 across a large 12-hospital Midwest healthcare system.

Methods

Context and Evidence synthesis

A COVID-19 evidence-based medicine (EBM) team was developed in March 2020 to rapidly review, catalogue, and publicly disseminate evidence related to proposed COVID-19 therapeutics including anticoagulation management.[16] Due to a lack of high-quality evidence from randomized controlled trials and the lack of expert guidelines, the EBM team developed a novel rubric to grade COVID-19 evidence.[17] Using this rubric, a multidisciplinary team including: COVID-19 physicians, LHS researchers, pharmacists, public health epidemiologists, and medical librarians reviewed and graded the evidence to date for anticoagulation in COVID-19.

CPG development

Guided by the EBM team's recommendations, system hematology service line leads (S.S., M.R.) oversaw the development of a CPG in collaboration with national hematology experts (Supplemental Figure 1). This CPG was initially disseminated beginning April 9, 2020. Significant

controversy existed at the time in the appropriate anticoagulation strategy with some studies suggesting no anticoagulation (*conservative treatment approach*) due to concerns for bleeding and disseminated intravascular coagulopathy to some studies suggesting tPA infusions (*aggressive treatment approach*) for patients with severe respiratory failure.[8,18] Ultimately, the CPG adhered to a "middle of the road" approach by instituting universal prophylactic weight-based anticoagulation for all patients. Similar to anticoagulation CPGs for other disease processes[19], we incorporated a risk stratification model whereby the intensity of anticoagulation was increased to moderate intensity (0.5 mg/kg BID enoxaparin or low intensity heparin infusion in case of renal failure) for patients with history of thrombosis, cancer, admission to intensive care unit or D-dimer >10 times the upper limit of normal. The CPG is a "living" framework, and has since undergone several iterations of modifications (up-stratification of patients with prior history of deep venous thrombosis, cancer, ICU patients, and exclusion of pregnant patients) based on evolution of the evidence.

CDS Development, Dissemination, and Implementation

The COVID-19 anticoagulation CPG CDS system was developed by the M Health Fairview clinical informatics development team (K.K., P.W.) in collaboration with the Associate CMIO for CDS (S.S.) in May 2020. Supplemental Figure 2 displays a process map for the CDS system. In brief, the CDS solution includes (representative screenshots displayed in Supplemental Figures 3 and 4):

- Tiered anticoagulation orderset
- Passive "reminder" of the anticoagulation CPG for COVID-19 patients without anticoagulation orders displayed in the EHR admission and transfer navigator
- Three "triggers" which activate interruptive alerts
- Various interactive and interruptive alerts

The interruptive BPAs were essentially "safety checks" to surveil if patients were on venous

thromboembolism (VTE) chemoprophylaxis on admission or if criteria for VTE-risk changed (e.g. increase in D-dimer above threshold or transfer to ICU) and only triggered for providers with ordering privileges. To ensure the BPA would not trigger for patients that have recovered from COVID-19 an infection status of *Recovered COVID-19* was built into the EHR.

Development, dissemination, and implementation followed our system protocol SCALED (SCaling AcceptabLE cDs) for CDS user-centered design, pilot testing, scaling, and evaluation. Prior to pilot testing, the CDS underwent iterative user interface / user experience (UI/UX) improvement during May. The CDS was piloted on May 14, 2020 and scaled on May 24, 2020. To support adoption and usability, a discipline-specific CDS dissemination strategy was carried out in May 2020 (Figure 1). To ensure embeddedness of the CDS in provider and pharmacist work-flow dissemination overlapped with implementation for 1 month follow “go-live”. Specific dissemination strategies included:

Providers:

- The CDS was presented to the intensivist, hospital medicine and primary care practice groups via formal didactic
- Our system utilized a daily workflow document for intensivists and hospital medicine providers caring for COVID-19 patients representing best practices, recent publications, and ongoing trials. The anticoagulation CDS was integrated into this workflow document and remained as a constant on this document throughout the entire implementation period.
- In the university setting CDS was presented at grand rounds at divisional, departmental and medical school platforms

Pharmacy:

- The CDS was presented routinely at the System-wide Anticoagulation Committee

All:

- Our system utilized a COVID-19 intranet COVID-19 resource page. This CDS was placed

within the system guidelines for management of COVID-19 patients

- The CDS was also posted on the University of Minnesota EBM COVID-19 webpage, on a public facing webpage for COVID-19 evidence-based practice geared towards clinicians

Data extraction and evaluation

Members of the study team (C.J.T., G.M.M., M.U.) developed a COVID-19 Datamart to facilitate near real-time evaluation of the CDS. Structured Query Language was used to automate daily export of COVID-19 EHR data into the data repository. A preprocessing pipeline was developed and implemented using Python 3.7.3. and Stata 16 to generate a flat file for each patient including patient anticoagulation risk stratification, tier of anticoagulation received, reach, adherence, clinical outcomes (in-hospital and out of hospital mortality, complications, ICU admission, and mechanical ventilation), comorbidities, home medications, inpatient medications received (e.g. remdesivir, tocilizumab, steroids, etc.), daily laboratory and vitals data, and demographics. Logicstream Health (Minneapolis, MN), an analysis platform for EHR content, was utilized to evaluate orderset, passive, and interruptive alert utilization.

CDS RE-AIM Evaluation

A pre-planned 6 month implementation evaluation was conducted guided by the RE-AIM framework.

Reach was defined as the number of patients admitted each month that received CDS (CDS Reach) or appropriate anticoagulation (CPG Reach) (numerator) over the number of patients admitted each month with COVID-19 (denominator). These two definitions of reach were defined to facilitate internal performance monitoring. For example, the state where CPG reach is high but CDS reach is low represents integration of the CPG into normal workflow without the need for CDS.

Adoption was defined at the implementation site and nursing unit level as the number of

patients admitted each month that received guideline concordant anticoagulation therapy (numerator) over the number of patients admitted each month with COVID-19 (denominator). It was not possible to define adoption accurately at the provider level as we were unable to assign a single provider responsible for a patient's initial care. Patient's receive orders from a variety of provider types including housestaff, advanced practice providers (APPs), or attending physicians either within the ED or by the inpatient team and thus we are unable to assign a single provider responsible for CPG adherence.

An *implementation* evaluation was conducted to investigate the effect of various CDS alert methods (passive and/or interruptive alerts) on anticoagulation CPG adherence. *Adherence* was defined at the patient level as receiving guideline concordant care within 24 hours of admission. Additionally, CPG fidelity was evaluated for each VTE risk stratification (Supplemental Figure 1).

To evaluate *maintenance*, following a wash-out period without any continued dissemination, we evaluated adherence during months 5 and 6 post implementation.

Statistical Approach:

To evaluate *effectiveness*, the association of CPG adherence on admission (at the patient level) with clinical outcomes was assessed via multiple methods:

(a) Multivariable logistic regression for binary dependent variables and negative binomial regression for continuous variables with a skewed distribution (hospital length of stay) using all 2406 patients that either received adherence care (n = 1,650) or did not receive adherent care (n = 853). All models were risk-adjusted using the confounding variables included below.

(b) 1:1 nearest neighbor propensity score matching was used to create cohorts of patients that received CPG adherent care (exposure or treatment of interest). Univariate logistic regression was then used to compare the need for ICU admission within 48 hours (primary outcome) for patients who received (vs did not receive) CPG adherent care on admission (exposure). Kaplan-Meier curves

were also estimated via a time-to-event analysis (censored at 48 hours following hospital admission) and compared using the log-rank test.

Propensity scores were estimated with logistic regression using the confounding variables listed below. Two evenly matched groups were formed with the common caliper set at 0.01. Following matching there were 1342 patients included (671 patients in each propensity-matched cohort). Standardized difference (SD) was evaluated prior to and after propensity matching to ensure that SD was < 0.1 in the propensity-matched cohort for each confounding variable (Supplemental Table 1). The distribution of propensity scores was well balanced between propensity-matched cohorts (Supplemental Figure 5).

(c) To account for the competing risk of death prior to ICU admission by 48 hours which occurred in 5 patients, a competing risk regression model (censored at 48 hours following hospital admission) was also fit in the propensity-matched cohort. Cumulative incidence curves were also estimated. Due to the importance of age as a confounding variable, age-stratified cumulative incidence curves were also generated.

The primary clinical outcome for the above models was the need for ICU admission within 48 hours of hospital admission. This endpoint was chosen clinically as the primary outcome because adherence with anticoagulation best practices is hypothesized to reduce micro and macrothrombosis events and minimize progression of disease and critical illness.

Secondary outcomes of interest for the above models were also evaluated, including: all-cause in-hospital mortality, the need for ICU admission at any time during hospitalization, the need for mechanical ventilation, hospital length of stay, the development of VTE or bleeding complications. Additionally, a binary composite outcome metric was developed and coded as positive if a patient had an all-cause in-hospital mortality, required ICU admission, required mechanical ventilation or required a hospital length of stay greater than 7 days.

Exposure/Treatment: The exposure or treatment of interest for the above models was defined

as a binary variable if patients received guideline adherent care on hospital admission

Confounding Variables for the above models: Variables known to be associated with the outcome of more severe COVID-19 infection (defined as requiring ICU admission or mechanical ventilation) were included as confounding variables for all analyses. This list of variables was developed by our team of subject matter experts with clinical and research expertise managing patients with Covid-19. All models were risk-adjusted to account for patient-level baseline demographics (age, gender, race/ethnicity, English vs non-English speaking, and area deprivation index [a marker of neighborhood socioeconomic status][20]), month of admission, in-hospital treatments for COVID-19 (remdesivir, tocilizumab, and steroids), body mass index (BMI), Elixhauser comorbidity index, the most aberrant vital signs within the first 24 hours of hospital admission (minimum saturation/FiO2 ratio, minimum systolic blood pressure, maximum respiratory rate), the initial hospital of treatment, and the source of admission (home, emergency department [ED], skilled nursing facility, intra-hospital transfer, prescheduled admission for surgery, admission from clinic/office appointment).

Subgroup analysis: Of the 2,503 patients, initial D-dimer, C-reactive Protein, creatinine, and absolute neutrophil-absolute lymphocyte ratio (NLR) were present for 1,181 patients. As these laboratory values have been shown on admission to be predictive of worse clinical outcomes[21-23] a secondary analysis was conducted in these 1,181 patients.

Data missingness: Overall missingness was low (< 2.04% for any individual variable with 3.9% of patients missing at least 1 covariate). Given the low rate of missingness, imputation was deemed unnecessary.[24]

Statistical analyses were performed using Stata MP, version 16 (StataCorp, College Station, TX). Statistical significance was defined as a p-value < 0.05.

Results

2,503 patients required in-hospital admission during the study period with PCR confirmed COVID-19 (Supplemental Figure 6). The median age was 64.9 years (IQR: 48.4 – 77.7 years). 1,180 (47.14%) of patients were male, and 262 (10.5%) of patients had an in-hospital death. Baseline characteristics of the patients that received CPG adherent (verses non-adherent) care are shown in Table 1. Similarly, baseline unadjusted clinical outcomes by CPG adherence are shown in Supplemental Table 2.

Table 1 – Patient Characteristics	Did not receive adherence anticoagulation	Received adherence anticoagulation	p-value
N	853	1650	
Demographics			
Age, median(IQR)	60.1 (35.2-75.7)	66.2 (52.7-78.4)	<0.001
Race, n(%)			0.6
White	476 (55.8%)	945 (57.3%)	
Black	117 (13.7%)	187 (11.3%)	
Asian	105 (12.3%)	211 (12.8%)	
Hispanic	62 (7.3%)	114 (6.9%)	
Declined	74 (8.7%)	161 (9.8%)	
Other	19 (2.2%)	32 (1.9%)	
Male, n(%)	350 (41.0%)	830 (50.3%)	<0.001
ADI quintile, n(%)			
0-19%	168 (19.7%)	312 (18.9%)	0.58
20-39%	256 (30.0%)	499 (30.2%)	
40%-59%	231 (27.1%)	478 (29.0%)	
60%-79%	114 (13.4%)	227 (13.8%)	
80%-100%	84 (9.8%)	134 (8.1%)	
Non-English Speaking, n(%)	233 (27.3%)	477 (28.9%)	0.40
Comorbidities / Clinical Characteristics			
Elixhauser Comorbidity Index, median(IQR)	4.0 (1.0-8.0)	5.0 (2.0-8.0)	<0.001
Body Mass Index, median(IQR)	28.6 (24.6-33.6)	29.8 (25.7-35.4)	<0.001
Lowest SBP in first 24 hours (mmHg), median(IQR)	111.0 (98.0-124.0)	113.0 (100.0-127.0)	0.01
Highest RR in first 24 hours (bpm), median(IQR)	22.0 (18.0-29.0)	24.0 (20.0-32.0)	<0.001
Lowest S/F ratio in first 24 hours, median(IQR)	438.1 (320.0-459.5)	355.6 (286.4-447.6)	<0.001
Initial D-Dimer, median(IQR)	1.2 (0.7-2.3)	1.1 (0.6-2.0)	0.02
Initial CRP, median(IQR)	64.3 (24.0-125.0)	72.0 (30.8-132.0)	0.18
Initial Creatinine median(IQR)	1.0 (0.8-1.4)	1.0 (0.8-1.3)	0.39
Initial NLR, median(IQR)	5.1 (3.1-8.4)	4.9 (3.0-8.6)	0.97
Received Remdesivir, n(%)	203 (24.2%)	843 (51.1%)	<0.001
Received Tocilizumab, n(%)	26 (3.0%)	90 (5.5%)	0.007
Received Steroids, n(%)	153 (17.9%)	575 (34.8%)	<0.001
Other Characteristics			
Admission Month of 2020, n(%)			0.06
March	18 (2.1%)	20 (1.2%)	
April	64 (7.5%)	103 (6.2%)	
May	90 (10.6%)	238 (14.4%)	

June	51 (6.0%)	103 (6.2%)	
July	65 (7.6%)	121 (7.3%)	
August	100 (11.7%)	159 (9.6%)	
September	70 (8.2%)	112 (6.8%)	
October	143 (16.8%)	291 (17.6%)	
November	252 (29.5%)	503 (30.5%)	
Implementation Site, n(%)			
Hospital 0	13 (1.5%)	59 (3.6%)	<0.001
Hospital 1	14 (1.6%)	26 (1.6%)	
Hospital 2	182 (21.3%)	363 (22.0%)	
Hospital 3	12 (1.4%)	21 (1.3%)	
Hospital 4	18 (2.1%)	51 (3.1%)	
Hospital 5	134 (15.7%)	268 (16.2%)	
Hospital 6	135 (15.8%)	264 (16.0%)	
Hospital 7	56 (6.6%)	163 (9.9%)	
Hospital 8	58 (6.8%)	50 (3.0%)	
Hospital 9	110 (12.9%)	148 (9.0%)	
Hospital 10	72 (8.4%)	152 (9.2%)	
Hospital 11	49 (5.7%)	85 (5.2%)	
Source of Admission, n(%)			<0.001
Home	391 (46.0%)	672 (40.8%)	
ED	374 (44.0%)	815 (49.5%)	
SNF	36 (4.2%)	62 (3.8%)	
External Hospital Transfer	33 (3.9%)	87 (5.3%)	
Admission for Surgery	8 (0.9%)	1 (0.1%)	
Clinic	8 (0.9%)	11 (0.7%)	

Legend**:** Patient characteristics by adherence with the anticoagulation guideline. Pearson chi-squared test was used to compare categorical and binary variables. Wilcoxon rank-sum test was used to compare continuous variables with a skewed distribution.
Abbreviations**:** IQR, interquartile range; ADI, area deprivation index; SBP, systolic blood pressure; RR, respiratory rate; S/F, oxygen saturation to fraction of inspired of oxygen ratio; CRP, C-reactive protein; NLR, neutrophil to lymphocyte ratio; ED, emergency department; SNF, skilled nursing facility

Reach

Figure 2 displays the reach of the CPG by month. Reach was purposefully measured in two ways (CPG reach or CDS reach). CPG reach was measured by the percentage of patients that received appropriate anticoagulation. CDS reach was measured by the percentage of patients whose providers received a CDS “reminder” to adhere to the CPG (Figure 2). Figure 2 displays the combined CPG and CDS reach (blue line) compared with CDS reach alone (red line). In the ideal setting, reach (blue line) would approach 1.0 and the CDS reach (red line) would approach 0. This would represent the state where all patients were receiving adherence without the need for interruptive CDS and would reflect complete uptake of the CPG by providers. Baseline reach of the anticoagulation CPG in April was approximately 61%. System-wide implementation of a CDS strategy in May resulted in 97% reach. The reduced triggering of the CDS after August represents

increased ordering of any anticoagulation for COVID-19 patients.

CPG reach improved following implementation of the CDS. CPG reach peaked during piloting and scaling of the CDS with an adherence rate of 74.4%. In the 6 months since scaling, adherence has averaged 67% (Figure 3).

Effectiveness

The *primary hypothesis* tested was if adherence with the anticoagulation CPG on hospital admission was associated with a reduced need for ICU management by 48 hours. Adherence with the anticoagulation CPG was independently associated with reduced need for ICU admission within 48 hours of hospital admission on multivariable logistic regression analysis (OR 0.39, 95% CI 0.30 – 0.51, $p < 0.001$) (Table 2 and Supplemental Table 3). In the propensity-matched cohorts, patients that received adherent care on admission with the CPG guideline had a 21.46% incidence of ICU admission within 48 hours compared with 34.28% for patients that did not receive adherent care on admission (Chi-squared $p<0.001$, logistic regression OR: 0.52, $p < 0.001$. A time-to-event analysis was also conducted. Patients that received adherent care on admission (vs patients that did not) were more likely to not require ICU admission by 48 hours, Log-rank test $p < 0.001$. (Supplemental Figure 7). 5 patients died prior to 48 hours and thus to account for this competing risk, a competing risk-regression analysis was conducted. Patients that received adherence with the CPG on admission had significantly reduced hazards for ICU admission by 48 hours when accounting for the competing risk of death. (SHR 0.58, $p < 0.001$). Cumulative incidence functions are provided in Supplemental Figure 8. As older patients may elect for comfort measures and die on the hospital ward in lieu of aggressive ICU cares, an age-stratified cumulative incidence function is provided in Supplemental Figure 9.

Secondary outcome analysis identified that adherence with the anticoagulation CPG was associated with reduced need for ICU admission at any point during hospitalization (OR 0.53, 95% CI 0.42 – 0.69, $p < 0.001$), and reduced all-cause in-hospital mortality (OR 0.67, 95% CI 0.48 – 0.94,

p = 0.019) (Table 2). Adherence with the anticoagulation CPG significantly reduced the odds of death, ICU admission, requirement for mechanical ventilation, or hospital length of stay greater than 7 days (OR 0.75, 95% CI 0.60 – 0.94, p = 0.01). Adherence with the anticoagulation CPG was independently associated with reduced bleeding complications (OR 0.39, 95% CI 0.21 – 0.72, p = 0.003), but not VTE complications (OR 0.87, 95% CI 0.65 – 1.17, p = 0.4). Adherence with the anticoagulation CPG was independently associated with an increased hospital length of stay (IRR 1.15, 95% CI 1.08 – 1.22, p < 0.001). This effect persisted when excluding patients that suffered an in-hospital death (IRR 1.13, 95% CI 1.06 – 1.2, p < 0.001). None of the other secondary analysis reached statistical significance (Table 2).

Table 2 – Likelihood of Adherence with CPG via multivariable logistic regression	Odds Ratio for CPG Adherence (vs. non-Adherence)	95% CI	p-value	C-statistic
Model 1 – Risk Adjustment without initial labs (n = 2,406)				
ICU Admission within 48 hours	0.39	0.3-0.51	<0.001	0.87
ICU Admission	0.53	0.42-0.69	<0.001	0.87
Required Mechanical Ventilation	1.18	0.79-1.77	0.4	0.93
All-Cause In-Hospital Mortality	0.67	0.48-0.94	0.019	0.88
Composite Outcome	0.75	0.60-0.94	0.013	0.82
VTE Complication	0.87	0.65-1.17	0.4	0.79
Bleeding Complication	0.39	0.21-0.73	0.003	0.83
Model 2 – Risk Adjustment including initial labs (n = 1,181)				
ICU Admission within 48 hours	0.28	0.19-0.43	<0.001	0.90
ICU Admission	0.44	0.29-0.64	<0.001	0.89
Required Mechanical Ventilation	1.2	0.67-2.2	0.5	0.94
All-Cause In-Hospital Mortality	0.92	0.56-1.52	0.7	0.88
Composite Outcome	0.61	0.42-0.87	0.006	0.82
VTE Complication	1.05	0.64-1.71	0.9	0.81
Bleeding Complication	0.47	0.17-1.26	0.1	0.87

Legend: Composite Outcome defined as need for ICU admission, mechanical ventilation, all-cause in-hospital mortality, or hospital length of stay greater than 7 days. C-statistic or concordance statistic was calculated for each model.
Abbreviations: ICU, intensive care unit; VTE, venous thromboembolism; CPG, clinical practice guideline; CI, confidence interval

In the model that included initial D-dimer, CRP, Creatinine and NLR, adherence with the anticoagulation CPG was independently associated with reduced need for ICU admission within 48 hours of hospital admission (OR 0.28, 95% CI 0.19-0.43, p < 0.001) or the need for ICU admission at any time during hospitalization (OR 0.44, 95% CI 0.29 – 0.64, p < 0.001) (Table 2). Adherence with the anticoagulation CPG significantly reduced the odds of death, ICU admission, requirement

for mechanical ventilation, or hospital length of stay greater than 7 days (OR 0.61, 95% CI 0.42 – 0.87, p = 0.006). Adherence with the anticoagulation CPG was independently associated with an increased hospital length of stay (IRR 1.12, 95% CI 1.03 – 1.22, p = 0.008). This effect persisted when excluding patients that suffered an in-hospital death (IRR 1.1, 95% CI 1.004 – 1.2, p = 0.04). None of the other secondary analysis reached statistical significance (Table 2).

Adoption

To investigate adoption rates across the system, we evaluated adoption by hospital. Our system includes 12 hospitals, 2 university settings that include resident and fellow trainees, 2 COVID-19 cohorting hospitals[25] staffed by attending physicians and advanced practice providers, and 8 community hospitals staffed by attending physicians and advanced practice providers. Adoption was highest at the COVID-19 cohorting hospitals and lowest at the university hospitals (Supplemental Figure 10). Variability was similarly noted across nursing units (Supplemental Figure 11). No discernable difference was noted in adoption analyses done by patient race/ethnicity, encounter type, or PUI status on admission (versus known COVID-19).

Implementation and Maintenance

Adherence was evaluated in the context of CDS. Adherence when CDS was delivered was 70% as compared to 62% without CDS (OR 1.43, 95% CI 1.2-1.7, p<0.001).

The CDS 5 Rights Framework recommends delivery of CDS at the “right” time in workflow. Four passive CDS elements were included to facilitate CPG adherence within various areas of the EHR and clinical workflow. For example, passive CDS was delivered within EHR navigators used during the admission, discharge, or transfer (ADT) workflow, during the rounding navigator, and within the general EHR order environment. Adherence with anticoagulation was highest when these passive elements were integrated within the Admission (75%), Rounding (75%), or Transfer (80%) Navigators (Supplemental Figure 12) compared when outside of an EHR care navigator (57%).

We then sought to investigate the relationship between adherence and passive verses

interruptive CDS intervention formats. 1,423 (57%) of patients had no CDS elements passive or interruptive. 699 patients had passive only CDS delivered to providers (27.9%), 111 patients had interruptive only CDS delivered to providers (4.4%), and 270 patients had a combination of passive and interruptive CDS delivered to providers (10.79%). The combination of passive CDS and interruptive alerts was associated with the highest adherence with the anticoagulation CPG (Supplemental Figure 13).

Variation in adherence was noted across baseline risk-groups. Patients in the moderate-risk group were less likely to receive adherence care (59.6%) compared with patients in the high (65%) and low risk groups (71%). Following implementation wash-out maintenance stabilized at 67% in months 5-6 (October-November 2020).

Discussion

This study represents a completed iteration of the continuous LHS cycle.[26] Adherence with the anticoagulation CPG was associated with significantly improved clinical outcomes. Adoption improved following the delivery of the CPG within a CDS system. Despite these improvements, variation was found to exist in adoption across hospitals and units. Adoption was highest at hospitals specializing in treating patients with COVID-19 and was lowest in tertiary academic hospitals. An evaluation of CDS delivery methods identified the combination of passive and interruptive alerts was associated with the highest adherence rate.

This study provides an important and early example of a real-world application of the LHS during COVID-19, a period with surged clinical resources and uncertain evidence-base. Critical to our successes was the early development of a COVID-19 datamart that included highly granular structured and unstructured patient-level data. Integration with an EHR analysis solution (Logicstream Health) facilitated near real-time evaluation of CDS alert activities by providers.

Our healthcare system has a rigorous and validated protocol for the development,

implementation, scaling, and evaluation of user-centered CDS systems with over 20 use cases implemented each year overseen by various enterprise CDS committees. Typically the process of development, implementation and scaling requires months and in this case occurred in a matter of weeks. COVID-19 provided a heightened sense of urgency and purpose in healthcare research and quality improvement that resulted in rapid progress in CDS development. The dedicated EBM team facilitated prompt CPG updates in response to rapidly changing evidence. Augmented stakeholder engagement and buy-in from the informatics development teams was also a critical element for success. The combination of expedited access to fully pre-processed and analyzable EHR data updated daily along with extraordinary team engagement and stakeholder support were critical for rapid implementation.

Despite these successes, room for optimization was identified from this analysis. First, in an attempt to minimize alert fatigue, the CDS was initially designed to only trigger for patients with COVID-19 but not on anticoagulation. While successful for the months of June and July in achieving near 95% reach, based on the data presented in this study, we hypothesize providers became comfortable attempting to order anticoagulation independent of the orderset resulting in patients being on incorrect anticoagulation and preventing corrective triggering of the CDS. Others have shared this experience where an attempt to develop user-centered CDS minimizing alerts resulted in a system overly passive that it cannot change behavior.[27] Despite all the negative press for interruptive alerts, we were surprised that interruptive alerts and the combination of interruptive alerts and passive CDS were associated with improved adherence compared to passive CDS alone. It is possible due to the COVID-19 pandemic and augmented sense of unity and purpose between clinicians and QI researchers that interruptive alerts were received more favorably.

Second, we identified large variation in adoption across hospitals and nursing units. Our academic health system is unique in the sense that we created specialty cohorting hospitals for COVID-19 patients[25] needing care across our academic health medical center, which was staffed

by attending clinicians well versed with institutional guidelines. Despite the availability of the same resources at all sites, adoption of the CPG via the use of CDS was much lower at non-cohorting sites. Specifically we identified adoption was very poor at university sites where the majority of orders are placed by housestaff compared with advanced practice providers at other sites.

Third, following each LHS evaluation cycle (practice to data, P2D) it is imperative that positive findings are disseminated widely. We were surprised adherence did not improve following our interim effectiveness analysis in August 2020 which identified a significant and independent improvement in clinical outcomes with anticoagulation. The unified theory of acceptance and use of technology (UTAUT) posits that a key construct affecting technology use intention (in this case using the CDS) is performance expectancy.[28] Essentially, if the provider believes that the CDS will improve patient outcomes they will have higher intentions to use it. In response to this RE-AIM evaluation, we will pilot an education intervention for continuing medical education credit to sites with lower adoption and assess impact at our next PDSA cycle.

In the early phase of the pandemic, there was widespread confusion about the underlying pathogenic mechanism and its implications to patient outcomes leading to highly variable practice in the medical community. To date there is limited data in management approach for COVID-19 associated coagulatopathy (CAC) particularly in high risk critically ill populations and for patients that are either managed as outpatient or post hospital discharge.[29,30] As of the time of this writing there are 147 (32 U.S.) randomized trials ongoing or recently completed to assess different anticoagulation approaches in COVID-19.[31] Since the completion of this evaluation in December 2020, results of multiple COVID-19 anticoagulation randomized trials have since been published. While a formal review of the literature is outside the scope of this manuscript, controversy persists as two recently published open-label randomized trials offered conflicting evidence with one suggesting a lack of benefit from therapeutic-dose anticoagulation in critically ill patients[10]; however, the other identified significant improvement in survival and increased organ support-free days in non-

critically ill patients[9]. However, both these studies suffer from multiple limitations[32] and both evaluated therapeutic anticoagulation doses whereas our consensus guideline includes a tiered approach including intermediate anticoagulation for specific high-risk subsets. During the study period, our tiered approach recommended an intermediate-dose for critically ill patients. In March, 2021, the INSPIRATION trial reported its findings and did not identify an advantage of intermediate-dose vs prophylactic dose anticoagulation for critically ill patients with COVID-19.[33] While observational, this study provides additional support that adherence with a tiered approach for anticoagulation in patients with COVID-19 is associated with improved clinical outcomes and in our healthcare setting reduced bleeding complications. Interestingly, we noted adherence was associated with reduced bleeding but not VTE complications. This may suggest that this approach does not impact large vessel venous thromboembolism but improved outcomes overall suggest that patients may be developing fewer microvessel thrombi, causing less systemic complications that typically lead to ICU admissions and adverse outcomes.

COVID 19 is a global emergency; given a lack of robust/consistent guidelines from leading societies, institutions had to develop a local approach to create a uniform plan of care and approach for its implementation. This is specifically problematic in larger systems with multiple hospitals. Our health system was particularly vulnerable to this issue due to significant heterogeneity resulting from a recent merger (different instances of same EHR, heterogeneous administrative policies and site-specific management protocols). As described above, there were concerns for increased risk of bleeding and many individual practitioners in our system were apprehensive to order anticoagulation in patients with COVID-19 leading to variable VTE prevention strategies and adverse patient outcomes.

Our study suffers from several limitations. First, our institutional preference for implementation evaluation typically takes a mixed-methods approach. However, due to contact precautions surrounding COVID-19 and significantly increased provider workload it was not feasible

to perform qualitative analysis of staff. Thus, this represents a quantitative only approach which may not fully discern specific trends. To expand on hypotheses that arose from this research, a future direction includes a voluntary survey of healthcare providers (initiated December 14, 2020) surrounding their familiarity with COVID-19 institutional guidelines and their experiences interacting with the CDS. Survey question development was guided by UTAUT constructs for technology acceptance. Additionally, while we identified an association with adherence and effectiveness of anticoagulation, it is important to not misconstrue this analysis. We did not evaluate the association of anticoagulation versus none and its association on outcomes, but rather we evaluated adherence with this guideline versus none. Thus non-adherent patients could have been either receiving more or less aggressive anticoagulation than the comparison group. In our institution, adherence was associated with improved clinical outcomes; however, this may not be generalizable to other institutions with different baseline cultural practices for anticoagulation management. VTE and bleeding complications were extracted using structured electronic health record data. It is possible these events may be under-reported. Our relatively small cohort size (n=2503) and single healthcare system represent additional limitation of the study.

Conclusion

This study provides an early example of a real-world application of the LHS during COVID-19. With or without pandemic, there is a need for implementation of evidence-based practice that is most up-to-date. Traditionally, the biggest barrier to this effort is the need for making major changes in the workflow. With the widespread use of EHR and increasing consolidation of health care systems, application of CPGs through the use of a CDS can offer an easy tool for implementation without adding confusion related to workflow changes, thus bringing uniformity in care at every level in the system and hence impact quality of care and patient outcomes.

AUTHOR CONTRIBUTIONS:

Surbhi Shah - Study design, data collection, data analysis, data interpretation, writing, and critical revision.

Sean Switzer - Study design, data collection, data analysis, data interpretation, writing, and critical revision.

Nathan Shippee - Study design, data interpretation, writing, and critical revision.

Kathryn Kosednar - Study design, data interpretation, writing, and critical revision.

Pamela Wogensen - Study design, data interpretation, writing, and critical revision.

Emma Jones- Study design, data interpretation, writing, and critical revision.

Deborah Pestka - Study design, data interpretation, writing, and critical revision.

Sameer Badlani - Study design, data interpretation, writing, and critical revision.

Mary Butler- Study design, data interpretation, writing, and critical revision.

Brittin Wagner- Study design, data interpretation, writing, and critical revision.

Katie White - Study design, data interpretation, writing, and critical revision.

Joshua Rhein- Study design, data collection, data interpretation, writing, and critical revision.

Brad Benson- Study design, data collection, data interpretation, writing, and critical revision.

Mark Reding - Study design, data interpretation, writing, and critical revision.

Michael Usher- Study design, data collection, data analysis, data interpretation, writing, and critical revision.

Genevieve Melton-Meaux - Study design, data collection, data analysis, data interpretation, writing, and critical revision.

Christopher J. Tignanelli - Study design, data collection, data analysis, data interpretation, writing, and critical revision.

ACKNOWLEDGEMENTS AND CONTRIBUTIONS:

The authors gratefully acknowledge Fairview Health Services IT staff: Iva Ninkovic, Karl Koch, Phill Stokkeland, Sandy Soukup, and Eric Murray.

CONFLICT OF INTERESTS AND FUNDING SOURCES

This research was supported by the Agency for Healthcare Research and Quality (AHRQ) and Patient-Centered Outcomes Research Institute (PCORI), grant K12HS026379 (SS, CJT) and the National Institutes of Health's National Center for Advancing Translational Sciences, grant KL2TR002492. Additional support for MN-LHS scholars is offered by the University of Minnesota Office of Academic Clinical Affairs and the Division of Health Policy and Management, University of Minnesota School of Public Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of AHRQ, PCORI, or Minnesota Learning Health System Mentored Career Development Program (MN-LHS). This grant was also supported by the University of Minnesota CTSA grant UL1TR000114.

FIGURE TITLES AND LEGENDS

Figures

Figure 1: Overall Development, Dissemination, Implementation, and Evaluation strategy

Abbreviations: CPG, clinical practice guideline; CDS, clinical decision support; D2K, data to knowledge; K2P, knowledge to practice; P2D, practice to data

Figure 2: Average Implementation Reach by Month

Legend: Blue line represents the combined CPG (patient received adherent anticoagulation) and CDS reach (patient's ordering providers received CDS suggesting adherent anticoagulation) by month.

Red line represents only CDS reach.

Abbreviations: CPG, clinical practice guideline; CDS, clinical decision support

Figure 3: Average Implementation Reach by Month or Implementation Phase

(A) Average CPG reach by healthcare system by month (B) Average CPG reach by healthcare system by implementation phase

Abbreviations: CPG, clinical practice guideline; CDS, clinical decision support

Supplemental Figures:

Supplemental Figure 1: M Health Fairview COVID-19 Anticoagulation Clinical Practice Guideline

Supplemental Figure 2: Process map of M Health Fairview Clinical Decision Support System

Supplemental Figure 3: Screenshots of COVID-19 anticoagulation clinical decision support system's passive and interruptive elements

Supplemental Figure 4: Screenshots of COVID-19 anticoagulation clinical decision support system surveillance of appropriate anticoagulation prophylaxis

Supplemental Figure 5: Propensity score distribution in propensity-matched cohorts. Legend: Blue/Untreated refers to the propensity-matched patient cohort that did not receive CPG adherent care on hospital admission. Red/Treated refers to the propensity-matched patient cohort that did receive CPG adherent care on hospital admission.

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Supplemental Figure 7: Kaplan-Meier failure estimates (for ICU admission by 48 hours)

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Supplemental Figure 8: Cumulative incidence function of ICU admission by 48 hours

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Supplemental Figure 9: Age-stratified Cumulative incidence function of ICU admission by 48 hours

Legend: Age-stratified Cumulative incidence function of ICU admission by 48 hours for patients that received CPG adherent care vs those that did not receive CPG adherent care.

Supplemental Figure 10: Mean Adoption by Implementation Site

Supplemental Figure 11: Mean Adoption by Nursing Unit

Supplemental Figure 12: Adherence with anticoagulation CPG by passive CDS elements

Abbreviations: CPG, clinical practice guideline; CDS, clinical decision support; IP, inpatient

Supplemental Figure 13: Adherence with the anticoagulation CPG by CDS type

Abbreviations: CPG, clinical practice guideline; CDS, clinical decision support

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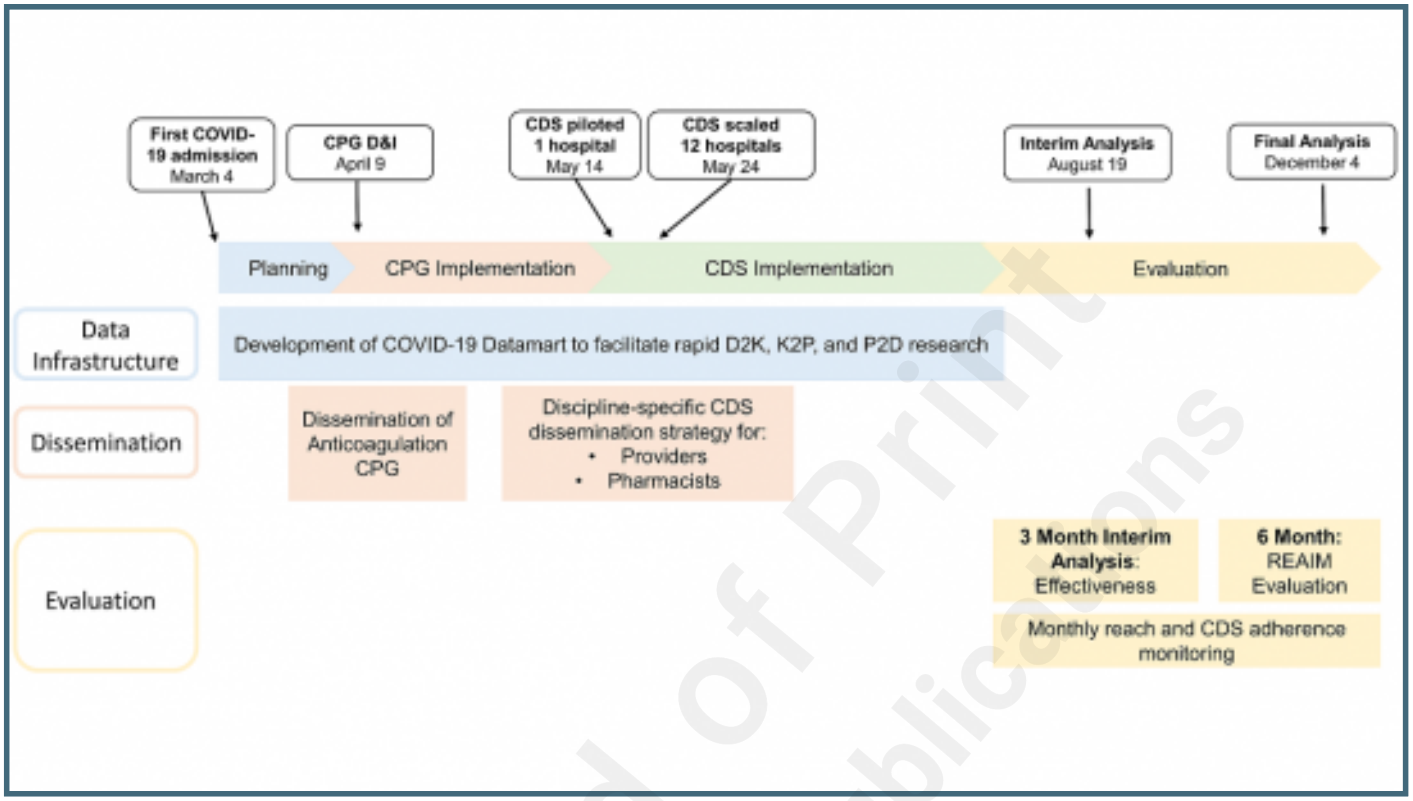
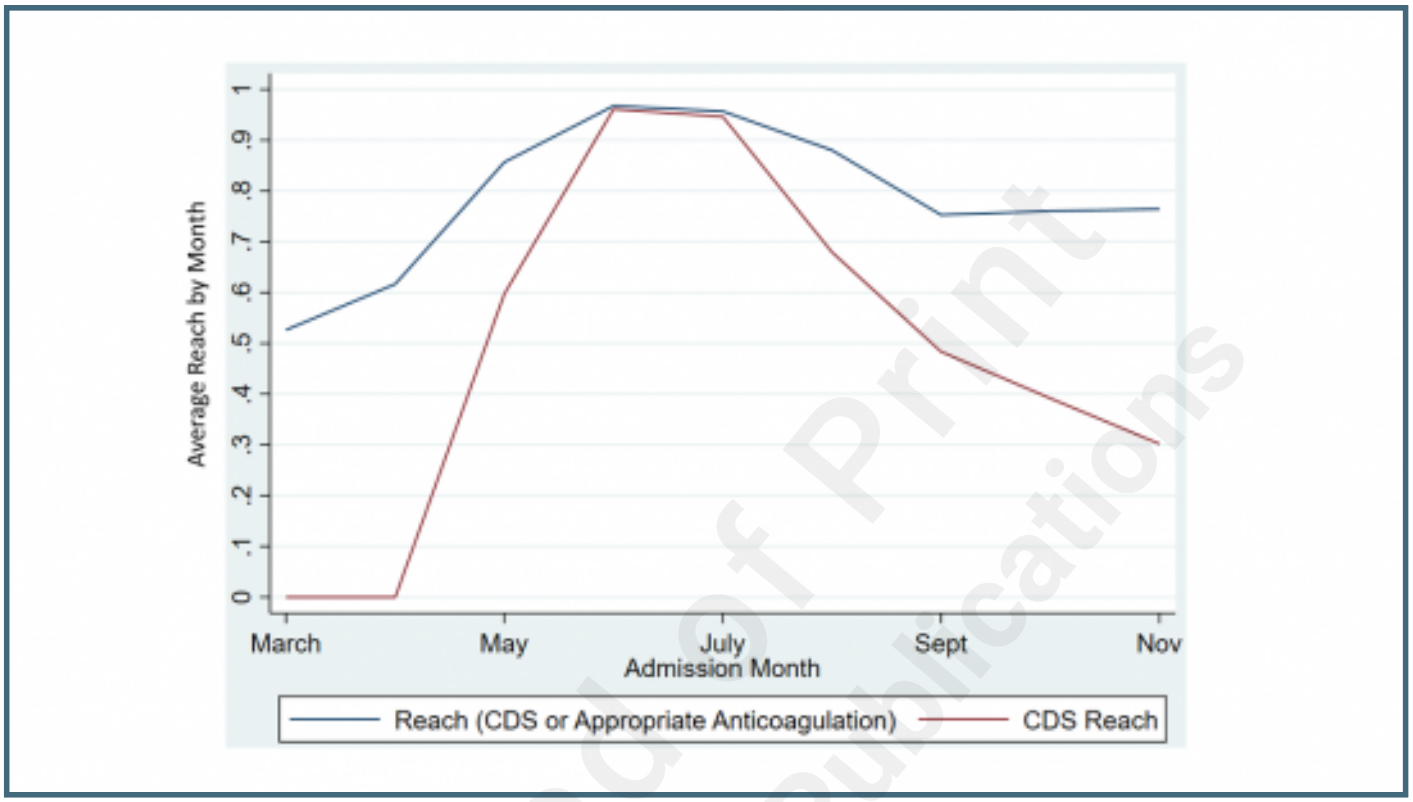
Supplementary Files

Figures

Overall Development, Dissemination, Implementation, and Evaluation strategy Abbreviations: CPG, clinical practice guideline; CDS, clinical decision support; D2K, data to knowledge; K2P, knowledge to practice; P2D, practice to data.



Average Implementation Reach by Month. Legend: Blue line represents the combined CPG (patient received adherent anticoagulation) and CDS reach (patient's ordering providers received CDS suggesting adherent anticoagulation) by month. Red line represents only CDS reach. Abbreviations: CPG, clinical practice guideline; CDS, clinical decision support.



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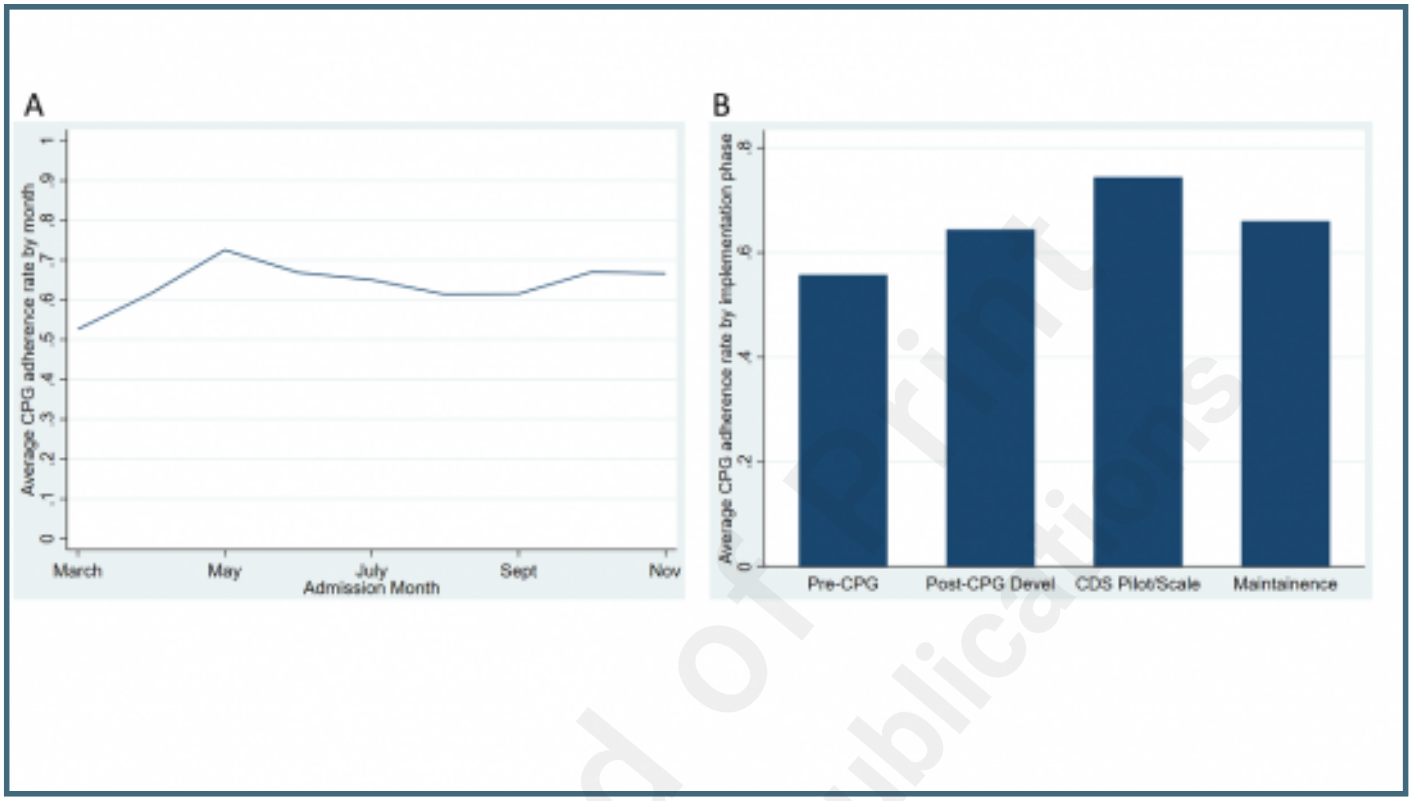

Multimedia Appendixes

M Health Fairview COVID-19 Anticoagulation Clinical Practice Guideline.
URL: http://asset.jmir.pub/assets/8b4c44ae32cfe1f7942a4fff008fba0d.png

Supplemental Figure 2: Process map of M Health Fairview Clinical Decision Support System.
URL: http://asset.jmir.pub/assets/18038e12710a35dec8e0d69a768f8ecc.png

Screenshots of COVID-19 anticoagulation clinical decision support system's passive and interruptive elements.
URL: http://asset.jmir.pub/assets/22618bcb353d395ae8b0422893ad8f00.png

Screenshots of COVID-19 anticoagulation clinical decision support system surveillance of appropriate anticoagulation prophylaxis.
URL: http://asset.jmir.pub/assets/70f6f28ce8e7ff8af82c01a459623c15.png

Supplemental Figure 5: Propensity score distribution in propensity-matched cohorts. Legend: Blue/Untreated refers to the propensity-matched patient cohort that did not receive CPG adherent care on hospital admission. Red/Treated refers to the propensity-matched patient cohort that did receive CPG adherent care on hospital admission.
URL: http://asset.jmir.pub/assets/ac26d75b125d0cebc59949fd48be6041.png

Study Diagram for selection of patients from COVID-19 inpatient database.
URL: http://asset.jmir.pub/assets/7193a3ec4850bc03da9fbb37a112fda4.png

Supplemental Figure 7: Kaplan-Meier failure estimates (for ICU admission by 48 hours) Legend: Kaplan-Meier failure estimates for patients that received CPG adherent care (red line) vs those that did not receive CPG adherent care (blue line).
URL: http://asset.jmir.pub/assets/3fce9d738158a3bf42fc526427e8d975.png

Supplemental Figure 8: Cumulative incidence function of ICU admission by 48 hours Legend: Cumulative incidence function of ICU admission by 48 hours for patients that received CPG adherent care (red line) vs those that did not receive CPG adherent care (blue line).
URL: http://asset.jmir.pub/assets/09975eb2a6839ccf45026bacd3afadc3.png

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URL: http://asset.jmir.pub/assets/540a0cc4c288f7119b01a7cd146d10dd.png

Mean Adoption by Implementation Site.
URL: http://asset.jmir.pub/assets/04128de2a74ee1dab212887f2db858e6.png

Mean Adoption by Nursing Unit.
URL: http://asset.jmir.pub/assets/95e59ac2bcd26985916954f4b4680890.png

Adherence with anticoagulation CPG by passive CDS elements. Abbreviations: CPG, clinical practice guideline; CDS, clinical decision support; IP, inpatient.
URL: http://asset.jmir.pub/assets/9d5f8c5b94ed81d7192a946e21c7603c.png

Adherence with the anticoagulation CPG by CDS type. Abbreviations: CPG, clinical practice guideline; CDS, clinical decision support.
URL: http://asset.jmir.pub/assets/f71e453c0ffe29850d65922e40faf236.png

Supplemental Table 1: Propensity Score Standardized Differences prior to and after matching Legend: Standardized differences before and after nearest neighbor propensity score matching Abbreviations: SD, standardized difference; SBP, systolic blood pressure; RR, respiratory rate; S/F, Oxygen saturation to FiO2 ratio.
URL: http://asset.jmir.pub/assets/5546eede540e67ed78e4856a26869994.docx

Unadjusted Outcomes.
URL: http://asset.jmir.pub/assets/7b7ac13ccc3e8a00f89bc73d461e24b0.docx

Full model output for multivariable logistic regression evaluating the association of adherence with CPG on hospital admission with the need for intensive care within 48 hours.

URL: http://asset.jmir.pub/assets/c7b5ae87188c175726ab589272ed4dd7.docx