

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email editorial.bmjopen@bmj.com

BMJ Open

Impact of Electronic Clinical Decision Support on Adherence to Guideline Recommended Treatment for Hyperlipidemia, Atrial Fibrillation, and Heart Failure: Protocol for a Cluster Randomized Trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-019087
Article Type:	Protocol
Date Submitted by the Author:	09-Aug-2017
Complete List of Authors:	Kessler, Maya; Mayo Clinic Minnesota, Primary Care Internal Medicine Carter, Rickey; Mayo Clinic, Health Sciences Research Cook, David; Mayo Clinic College of Medicine, Division of General Internal Medicine Kor, Daryl; Mayo Clinic, Anesthesiology McKie, Paul; Mayo Clinic Minnesota Pencille, Laurie; Mayo Clinic, Office of Information and Knowledge Management Scheitel, Marianne; Mayo Clinic, Office of Information and Knowledge Management Chaudhry, Rajeev; Mayo Clinic, Division of Primary Care Internal Medicine and Knowledge Delivery Center
Primary Subject Heading:	Health informatics
Secondary Subject Heading:	General practice / Family practice, Cardiovascular medicine, Health services research
Keywords:	Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, Adult cardiology < CARDIOLOGY, INTERNAL MEDICINE

1
2
3 **TITLE:** Impact of Electronic Clinical Decision Support on Adherence to Guideline Recommended
4 Treatment for Hyperlipidemia, Atrial Fibrillation, and Heart Failure: Protocol for a Cluster Randomized
5 Trial
6

7
8 **AUTHORS**

9 Maya E. Kessler MD, MPH¹
10 Rickey E. Carter, PhD^{2,3}
11 David A. Cook, MD, MHPE^{4,5}
12 Daryl J. Kor, MD, MSc^{3,6}
13 Paul M. McKie, MD⁷
14 Laurie J. Pencille^{3,4}
15 Marianne R. Scheitel⁴
16 Rajeev Chaudhry, MBBS, MPH^{1, 4}
17

18
19 **AFFILIATIONS**

20 1 Department of Medicine, Division of Primary Care Internal Medicine, Mayo Clinic, Rochester MN,
21 USA
22 2 Department of Health Sciences Research, Mayo Clinic, Rochester MN, USA
23 3 Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester
24 MN, USA
25 4 Office of Information and Knowledge Management, Mayo Clinic, Rochester MN, USA
26 5 Department of Medicine, Division of General Internal Medicine, Mayo Clinic, Rochester MN USA
27 6 Department of Anesthesiology, Mayo Clinic, Rochester MN, USA
28 7 Department of Medicine, Division of Cardiology, Mayo Clinic, Rochester MN, USA
29

30
31 **CORRESPONDING AUTHOR**

32 Maya E. Kessler
33 200 First Street SW, Rochester MN, USA, 55905
34 Phone: 507-284-0945
35 Fax: 507-266-1799
36 kessler.maya@mayo.edu
37

38
39 **WORD COUNT**

40 3851
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

ABSTRACT

Introduction: Clinical practice guidelines facilitate optimal clinical practice. Point of care access, interpretation, and application of such guidelines, however, is inconsistent. Informatics-based tools may help clinicians apply guidelines more consistently. We have developed a novel clinical decision support tool that presents guideline relevant information and actionable items to clinicians at the point of care. We aim to test whether this tool improves the management of hyperlipidemia, atrial fibrillation, and heart failure by primary care clinicians.

Methods/analysis: Clinician care teams were cluster randomized to receive access to the clinical decision support tool or passive access to institutional guidelines on May 16th, 2016. The trial began on June 1st, 2016, when access to the tool was granted to the intervention clinicians. The trial will be run for six months to ensure a sufficient number of patient encounters to achieve 80% power to detect a two-fold increase in the primary outcome at the 0.05 level of significance. The primary outcome measure will be the percentage of guideline-based recommendations acted upon by clinicians for hyperlipidemia, atrial fibrillation, and heart failure. We hypothesize care teams with access to the clinical decision support tool will act upon recommendations at a higher rate than care teams in the standard of care arm.

Ethics and dissemination: The Mayo Clinic Institutional Review Board approved all study procedures. Informed consent was obtained from clinicians. A waiver of informed consent and of HIPAA authorization for patients managed by clinicians in the study was granted. In addition to publication, results will be disseminated via meetings and newsletters.

Trials registration: ClinicalTrials.gov Identifier: NCT02742545

STRENGTHS AND LIMITATIONS

Strengths

The main strength of this study is the design of the clinical decision support tool. The tool was developed with iterative clinician input to fit the work-flow. And it uses complex data in its algorithms (such as risk scores and information only available through natural language processing) to enable the provision of individualized treatment recommendations for patients with three distinct yet common cardiovascular conditions. Its efficacy will be evaluated with a rigorous study design using clinically meaningful endpoints.

Limitations

The main limitations are that the study may lack generalizability—as the clinician decision support tool is a proprietary system, not yet widely available, tested in an academic medical center.

BACKGROUND

Cardiovascular disease is the leading cause of morbidity and mortality in the United States.¹ Prevention and treatment guidelines for cardiovascular diseases aim to improve outcomes and cost effectiveness.²⁻⁴ However, successfully incorporating these guidelines into clinical practice remains a challenge.

Some of the largest gaps between evidence-based guidelines and clinical practice exist for the management of hyperlipidemia, atrial fibrillation, and heart failure.⁵ It is estimated that only 41% of the 61.8 million patients in the United States who are eligible for statins under the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines are receiving these medications.⁶ Of the 2.8 million patients with heart failure and left ventricular ejection fraction (LVEF) <40%, rates of compliance with the American College of Cardiology Foundation - American Heart Association (ACCF-AHA) guidelines are as low as 7.3% for some measures.⁷ Similarly for atrial fibrillation, guideline compliance is suboptimal.^{8,9}

Many interventions have been designed to address these gaps between evidence and practice, yet most achieve only minimal gains in guideline adherence.¹⁰ Although informatics-based clinical decision support tools have shown promise, most interventions aimed at improving the medical management of cardiovascular disease have shown only minimal gains in compliance to recommended treatment, with a recent systematic review showing a median improvement of 2.0% across interventions.¹¹ Among studies looking at interventions aimed at improving prescribing practices for hyperlipidemia, atrial fibrillation, and heart failure, results ranged from no effect to 13.3% improvement.¹²⁻¹⁵ The most successful intervention was unique in that the tool provided clinicians with all the information needed to make a decision within the application. None of the algorithms used by the tools were particularly sophisticated in their ability to take into account common clinical conditions that might alter treatment recommendations. Only two of the four interventions were integrated into the electronic medical record (EMR).

Using the lessons learned from these studies and also from other studies of clinical decision support for chronic disease management,¹⁶⁻¹⁸ we devised a tool that took into account individual patient factors that might alter treatment recommendations and presented these factors along with calculated risk scores, decision aids, and educational materials when a treatment recommendation was made. Clinician input was sought throughout the design process and when deciding on how to integrate the tool into the clinician workflow.

In this paper, we first describe the development of this clinical decision support tool, MayoExpertAdvisor, and then outline the protocol for an ongoing clinical trial to formally evaluate its effectiveness. We hypothesize that MayoExpertAdvisor will increase clinician adherence to best practice treatment recommendations for patients with hyperlipidemia, atrial fibrillation and heart failure

DEVELOPMENT AND VALIDATION OF MAYOEXPERTADVISOR

Like many institutions, Mayo Clinic develops and implements institution-wide guidelines to standardize patient care. Mayo Clinic's care process guidelines incorporate expert opinion, best practices supported by professional organizations, and local standards of care while allowing for individualization of treatment. These guidelines are available to Mayo Clinic clinicians through a multifaceted computer-based tool called AskMayoExpert. AskMayoExpert is available via local Intranet to all clinicians at Mayo Clinic and its affiliated health care organizations. While the knowledge contained in such care process guidelines is a useful reference for clinicians, a fundamental challenge is faced when clinicians must look up data within the electronic medical record (EMR) and/or calculate risk scores to apply care algorithms.^{19,20} As an adjunct tool to complement AskMayoExpert, MayoExpertAdvisor was developed to automate these tasks. MayoExpertAdvisor pulls data from the EMR and calculates risk to determine appropriate care. It then notifies the clinician when care differs from the guidelines by delivering action-oriented recommendations, along with a brief justification, in real-time at the point of care. MayoExpertAdvisor is embedded in the EMR to facilitate integration into the clinical workflow.

institutional **Guidelines for Hyperlipidemia, Atrial Fibrillation, and Heart Failure**

Using the process described above, institutional guidelines for management of hyperlipidemia, atrial fibrillation, and heart failure were developed. Publically available resources used as a basis for the guidelines are listed in Table 1. Generally, Mayo's institutional guidelines mirror nationally recognized best practices. For example, the institutional guideline for hyperlipidemia uses the 2013 ACC/AHA guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk as a starting point, but also incorporates other factors, such as the patients Framingham 30-year risk of atherosclerotic cardiovascular disease (ASCVD) and the use of a decision aid to discuss the pros and cons of statin therapy with a patient.^{21,22} The institutional guidelines used to develop MayoExpertAdvisor for hyperlipidemia, atrial fibrillation, and heart failure are included in Appendixes 1-3.

Table 1: Resources used for the Development of Institutional Guidelines

Condition	Sources
Hyperlipidemia	2013 American College of Cardiology/American Heart Association (ACC/AHA) guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk ³
	A Summary and Critical Assessment of the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Disease Risk in Adults ²¹
Atrial Fibrillation	2014 American Heart Association/American College of Cardiology/Heart Rhythm Society Guidelines for the Management of Patients with Atrial Fibrillation ²
Heart Failure	2013 American College of Cardiology Foundation/American Heart Association guideline for the management of heart failure ⁴

MayoExpertAdvisor Development

Operationally, MayoExpertAdvisor captures the patient-specific data required to determine appropriate care recommendations from the EMR and then presents relevant data alongside treatment suggestions to clinicians. To develop MayoExpertAdvisor, a team of clinicians and information technology (IT) experts worked together to translate the institutional guidelines into computational logic. Then, the IT team developed processes to automatically gather from the EMR the data needed to run the algorithms. For data not optimally captured from discrete sources (such as ICD-9 or 10 codes), natural language processing (NLP) was used. For example, common comorbidities were captured both from ICD-9 or 10 codes and from free text within problem lists. Some inputs such as alcohol use to determine bleeding risk were almost exclusively captured through NLP as this is not routinely coded in a discrete format by clinicians.

Clinicians worked with user experience designers to develop the user interface. A user-centered design process in which the team researched the needs of clinicians and aligned the design of the application to meet those needs was used. This process started with collaborative co-design working sessions, in which information needs and decision-making flows were elicited from clinicians, and user interface design concepts were created. Industry-best practice design principles for usability²³ were used throughout the design process. Once an initial design was agreed upon, the team conducted task-based usability testing to uncover any issues users might have in completing key tasks with the design. The user interface design was then revised based on the findings from this usability study to better meet user needs.

Validation of MayoExpertAdvisor

Level 1 – Receiving the correct data: MayoExpertAdvisor requires complex data sources, such as risk scores and information only retrievable through NLP. The accuracy of each data element needed to run MEA algorithms was tested until the error rate was less than 5% in 30 consecutive patient records.

Level 2 – Testing of the logic: MayoExpertAdvisor logic was tested on patients with hyperlipidemia, atrial fibrillation, and heart failure and the automated recommendations were compared to clinician chart

review. The IT team was notified when any discrepancies were found so that programming errors could be resolved. This process was repeated until no errors were observed in 200 patient records.

Level 3-Testing of User Interface: A formal usability study was conducted, in which twelve clinicians walked through clinical scenarios using a working MayoExpertAdvisor prototype. Clinicians were observed by a facilitator who recorded any difficulties noted and also asked clinicians a set of standardized questions at the end of each scenario and solicited general feedback about the tool. Based on study findings, the user interface was redesigned to address observed difficulties navigating the tool and clinician concerns. For example, there was a general lack of clarity among participants of where to look in the interface for which information. To address this issue, the information was reorganized around conditions rather than by type of information (e.g., care recommendations, risk scoring tools and knowledge resources) and the visual hierarchy of information was adjusted by changing font treatments and adding graphical elements such as icons to direct the user's vision. Another issue was users needing to see current therapies being used for the patient, but not having this information available in the tool. This was addressed by adding this information into the interface for each condition.

Level 4 – Pilot: MayoExpertAdvisor was tested in a clinical setting with 26 primary care physicians for four weeks. User feedback was informally solicited throughout the pilot and formally collected through a post-pilot survey. Survey results indicated clinicians were generally satisfied with the tool, but thought care recommendation notification process, though email, did not fit their work-flow. They also indicated they often did not follow a care recommendation due to a comorbidity not captured by the tool, with the most often cited comorbidity being statin intolerance. Additional capabilities for recognizing comorbidities were built into the tool after the pilot (i.e. identifying statin intolerance) and the tool was further integrated into the EMR through the additions of colored Mayo Expert Advisor alerts visible within the EMR that notified the clinician of the presence of a MayoExpertAdvisor recommendation.

MayoExpertAdvisor for Hyperlipidemia, Atrial Fibrillation, and Heart Failure

Clinicians are notified in several locations in the EMR when a recommendation is available for a patient (see Figure 1). When a clinician clicks on an alert or the MayoExpertAdvisor tab in the EMR, a screen opens that reveals the treatment recommendation along with relevant patient data, risk scores, decision aids, and educational materials (see Figure 2). Clinicians can manipulate patient data to visualize how life style modification (such as smoking cessation) or treatment changes (such as starting a drug or changing drug dose) will affect risk. These manipulations are only temporary and are not stored in MayoExpertAdvisor or in the EMR.

There are several treatment recommendations that MayoExpertAdvisor can give for each cardiac condition. For hyperlipidemia, MayoExpertAdvisor suggests a specific statin intensity. For atrial fibrillation, MayoExpertAdvisor decides in favor or against anticoagulation based on the CHA₂DS₂-VASc²⁴ and the HAS-BLED scores.²⁵ For heart failure MayoExpertAdvisor recommends (a) initiation of beta blocker therapy, (b) up-titration of beta blocker therapy, (c) initiation of ACE inhibitor/ARB therapy, (d) and up-titration of ACE inhibitor/ARB therapy. MayoExpertAdvisor also notes when patients with the above conditions are well managed according to institutional guidelines, but this does not generate an alert. For a detailed list of possible MayoExpertAdvisor recommendations please see Table 2.

Table 2: MEA Recommendations

Condition	Recommendations	
	Type	Text
Hyperlipidemia	Low to moderate intensity statin	Consider low- to moderate-intensity statin therapy due to diabetes and elevated cholesterol Consider moderate-intensity statin therapy due to diabetes and elevated risk Consider moderate-intensity statin therapy due to ASCVD (age >75) Consider moderate-intensity statin therapy due to elevated risk

	Moderate to high intensity statin	Consider moderate- to high-intensity statin therapy due to ASCVD Consider moderate- to high-intensity statin therapy due to LDL \geq 190 Consider moderate- to high-intensity statin therapy due to diabetes and elevated risk
	Lifestyle modification	Therapeutic lifestyle modifications recommended due to elevated triglycerides and risk of pancreatitis
	Fibrate/ omega 3	Fibrate and/or omega 3 therapy recommended due to elevated triglycerides and risk of pancreatitis
	Well managed	Lipids are controlled on current medication
Atrial fibrillation	No anticoagulation	No anticoagulation therapy indicated due to CHA2DS2-VASc score = 0
	Initiate Anticoagulation	Consider anticoagulation therapy, if HAS-BLED score <3, due to CHA2DS2-VASc score = 1 Consider anticoagulation therapy, if HAS-BLED score <3, due to CHA2DS2-VASc score 2 or greater
	Well managed	Patient on anticoagulant well-managed according to guidelines for management of atrial fibrillation
Heart Failure	Initiate beta blocker	Consider beta blocker due to heart failure
	Initiate ACE Inhibitor or ARB	Consider ACE inhibitor or ARB due to heart failure
	Titrate ACE Inhibitor or ARB	Consider increasing dose of ACE inhibitor or ARB to target dose for heart failure, monitor creatinine and potassium levels
	Titrate beta blocker	Consider increasing dose of beta blocker to target dose for heart failure
	Titrate aldosterone blocker	Consider increasing dose of aldosterone blocker to target dose for heart failure, monitor creatinine and potassium levels
	Medication contraindicated	Diltiazem contraindicated because of heart failure Verapamil contraindicated because of heart failure Nonsteroidal anti-inflammatory drugs contraindicated because of heart failure Rosiglitazone contraindicated because of heart failure Cilostazol contraindicated because of heart failure Itraconazole contraindicated because of heart failure Dronedaronone contraindicated because of heart failure Flecainide contraindicated because of heart failure Propafenone contraindicated because of heart failure
	Well managed	Patient is on appropriate dose of beta blocker Patient is on appropriate dose of ACE inhibitor or ARB Patient is on appropriate dose of aldosterone blocker.

METHODS

Study Design

MayoExpertAdvisor is undergoing evaluation in an ongoing cluster-randomized, un-blinded clinical trial with clinician care teams as the unit of randomization. If MayoExpertAdvisor is effective at the end of the trial it will be made available to both the intervention and control arm.

Setting

The study is being conducted at four geographically-distinct primary care practice sites affiliated with the Mayo Clinic in Rochester, Minnesota, an academic medical center.

Eligibility Criteria

All primary care clinicians (physicians, nurse practitioners, and physician assistants) practicing in the divisions of Family Medicine or Primary Care Internal Medicine at Mayo Clinic in Rochester, Minnesota were eligible to participate. Physicians in training (i.e., medical students and residents) were excluded. Patient data were used for determination of study outcomes. To be included for data extraction purposes, patients needed to have one of the specified clinical conditions and to be in the panel of one of the clinicians in the trial. All patients seen by eligible clinicians are Olmsted County residents and thus

1
2
3 the demographics reflect the local population. Patients who did not authorize the use of their medical
4 record for research were excluded.
5

6 7 **Recruitment of Clinicians**

8 Clinicians were recruited through presentations at division meetings, emails, phone calls, or by
9 individual face to face contact. If they indicated they were interested in participating, a meeting with a
10 study team member was scheduled to review the details of the study. Any individual who indicated they
11 did not wish to participate in the study was placed on a do not contact list and no further contact was
12 initiated. To avoid potential coercion, clinicians were not recruited by anyone in a supervisory or position
13 of perceived power over them.
14

15 16 **Randomization**

17 Clinicians were cluster randomized by care teams in order to minimize the potential
18 contamination that could occur if multiple members of a care team saw the same patient during the study
19 period. Care teams varied in size from 5-8 clinicians. There were twenty care teams representing three
20 practice types (Family Medicine, Internal Medicine, and combined Family Medicine and Internal
21 Medicine), located at four distinct clinical sites. Prior to randomization, these twenty teams were
22 stratified into six strata to create balance of practice type and physical location. There was one mixed
23 strata with three family medicine and one internal medicine care team pooled from two physical
24 locations; the remaining five strata were homogeneous in physical location and practice type. Each
25 stratum comprised two, four, or six care teams. A stratified, blocked randomization schedule was
26 generated by the study biostatistician (REC) to produce an equal number of care teams per condition
27 using a randomly generated code. The randomized assignments remained with the study biostatistician
28 until the study start, at which time access to MEA was granted, if applicable, and consented clinicians
29 were notified by study staff of the group assignment.
30

31 32 **Clinician Education (both groups)**

33 All clinicians received a 4 minute online educational module that reviewed the current
34 institutional guidelines for management of hyperlipidemia, atrial fibrillation, and heart failure.
35

36 37 **Intervention group**

38 Clinicians in care teams assigned to the intervention arm received training by the research team
39 on the use of MayoExpertAdvisor, were given access to MayoExpertAdvisor, and will be alerted of
40 MayoExpertAdvisor care recommendations throughout the study period.
41

42 43 **Control group**

44 Clinicians in care teams assigned to the standard of care arm continue to have access to
45 institutional guidelines through the AskMayoExpert knowledge resource, but do not have access to the
46 MayoExpertAdvisor screen. MayoExpertAdvisor recommendations are run in the background for data
47 collection purposes (see below), but control group clinicians do not have access to these
48 recommendations.
49

50 51 **Data Sources**

52 *Baseline Assessment:* The MayoExpertAdvisor algorithm was run on all eligible patient records at the
53 start of the study. The specific nature of the MayoExpertAdvisor recommendations for each patient (if
54 any) were recorded; if patients were already "well managed" this was also recorded. These data will be
55 used to assess the baseline adherence to the institutional guidelines for hyperlipidemia, atrial fibrillation,
56 and/or heart failure.
57

58 *Daily Pre-visit MayoExpertAdvisor Assessment of Patient Records:* The MayoExpertAdvisor algorithm
59 is applied to all eligible patients the evening prior to a scheduled outpatient visit. As with the baseline
60

1
2
3 assessment, the daily pre-visit assessment includes the specific nature of the MEA recommendations for
4 each patient and also which patients are well managed. These data will be used to assess the pre-visit
5 adherence to the institutional guidelines for hyperlipidemia, atrial fibrillation, and/or heart failure.
6

7
8 *Daily Post-visit MayoExpertAdvisor Assessment of Patient Record:* The MayoExpertAdvisor algorithm
9 is applied the evening after the visit to the same patients to whom the MayoExpertAdvisor algorithm was
10 applied the evening prior, and again extracts information about MayoExpertAdvisor recommendations for
11 each patient. This data will be used to assess the post-visit adherence to the institutional guidelines for
12 hyperlipidemia, atrial fibrillation, and/or heart failure.
13

14 *Study Completion MayoExpertAdvisor Assessment:* The MayoExpertAdvisor algorithm will be run on
15 all eligible patients at the completion of the study to provide a similar set of data as described for the
16 Baseline MayoExpertAdvisor Assessment.
17

18 *MayoExpertAdvisor Application Measures of Use:* Clicks to view MayoExpertAdvisor recommendations
19 are being tracked by standard timing and click metrics, and are stored as a component of the application's
20 operation.
21

22
23 *Survey Data:* A nine-item survey was sent to all study clinicians at the start of the study ascertaining a)
24 efficiency in managing the three clinical conditions; b) frequency of using risk scores in managing the
25 three clinical conditions, and c) the overall utility/burden of clinical decision support tools. The same
26 survey will be administered at 2-month intervals throughout the study. At the completion of the study, we
27 will ask clinicians in the intervention arm to complete a 25-item survey to evaluate their impressions of
28 MayoExpertAdvisor in domains of effectiveness, adoption, implementation, maintenance, usability, and
29 overall satisfaction. We will also solicit specific suggestions for improvement.
30

31 **Primary Outcome**

32 The primary endpoint is the percentage of guideline-based recommendations acted upon by
33 clinicians for hyperlipidemia, atrial fibrillation, and heart failure. We hypothesize that care teams with
34 access to MayoExpertAdvisor will provide more guideline-consistent care than care teams without access
35 to MayoExpertAdvisor.
36

37 **Secondary Outcomes**

38
39 Secondary endpoints include the following: (1) the percentage of pre-visit care process guideline
40 based recommendations acted upon by clinicians for each condition individually (i.e., hyperlipidemia,
41 atrial fibrillation, and heart failure); (2) the change in percentage of patients on optimal therapy for each
42 condition from the initiation to the completion of the study; (3) self-reported efficiency in managing the
43 three clinical conditions; (4) self-reported use of risk calculators; (5) overall utility/burden of clinical
44 decision support tools; (6) overall impressions of MayoExpertAdvisor in the domains of effectiveness,
45 adoption, implementation, maintenance, usability, and overall satisfaction; and (7) overall use of the
46 application
47
48
49
50

51 **Statistical Considerations**

52 *Primary Analysis:* The study design provides two levels of hierarchy in the data. First, the unit of
53 randomization was the care team, which includes multiple clinicians. The second level of hierarchy is the
54 individual clinician. For the purpose of the analysis, we expect that the variance component due to the
55 care team to be negligible, and potentially not estimable. Therefore, the primary endpoint will be tested
56 with a generalized estimating equation (GEE) model using an identity link and binomial distribution with
57 the clustering variable being the individual provider identification number. The primary parameter of
58
59
60

1
2
3 interest in this model will be the main effect of the MayoExpertAdvisor intervention. With the identity
4 link, the parameter estimate is interpretable as the change in percentage points of the primary outcome
5 between groups. The clustering will be incorporated into model by means of the robust variance estimator
6 using care team as the clustering indicator. As a sensitivity analysis, Rao-Cramer adjusted chi-square
7 tests will be computed to compare the primary outcome between interventions. In addition, the primary
8 outcome over time will be modeled using GEE to determine if temporal trends in the data are present.
9 Secondary endpoints will be tested using a similar analytical strategy. For the primary analysis, we will
10 assume that if a patient has more than one encounter in course of the study, that each of his or her
11 encounters is statistically independent. This is to address the potential lack of identifiability of multiple
12 encounters within patient due to the de-identification process as well as possible convergence issues with
13 the higher order hierarchical model.
14
15

16 *Sample Size Estimation:* The sample size calculations are based on the following factors: (1) target power
17 80%; alpha=0.05 (two-sided); no interim analysis / alpha-spending function; (2) randomization of
18 clusters: approximately 10 provider teams (clusters) to MayoExpertAdvisor and approximately 10
19 provider teams (clusters) to standard of care; (3) an estimate that 2% of the patient encounters that are not
20 exposed to the MayoExpertAdvisor will have a change in the care plan that would have been suggested
21 by information directly reported by the MayoExpertAdvisor system had it been available; (4) an estimate
22 that MayoExpertAdvisor will increase the percentage of patient encounters with a change in their care
23 plan to 4% (this change is consistent with the median change seen in a systematic review of similar
24 studies¹¹); and (5) an intraclass correlation (ICC) range between 0.005 and 0.0075 based on the pilot study
25 data. Based on these assumptions, the total number of patient encounters per cluster required is estimated
26 to be between 263 (ICC = 0.005) to 772 (ICC=0.0075). For study planning, the higher number is selected
27 such that the total sample size per arm is 7720 (15,440 total patient encounters). Assuming each care team
28 will have at least 20 patient encounters per clinic day, a minimum of 39 clinic days are expected for each
29 team. We conservatively estimate that it will take approximately 6 months to provide some protection
30 against the uncertainty of the ICC, variable staffing loads and vacation schedules over the summer, and
31 for sufficient time to monitor usage patterns over time. The total number of patient encounters during this
32 period of time cannot be determined with certainty and it is expected to vary by care team. The IRB
33 approval allows the protocol to utilize the first 50,000 patient encounters during the 6-month study period.
34
35
36

37 **ETHICS AND DISSEMINATION**

38 This research study was reviewed and approved by the Mayo Clinic Institutional Review Board.
39 The clinicians were deemed human subjects and written informed consent for their participation was
40 obtained. HIPAA authorization for clinicians did not apply. A waiver of informed consent and of HIPAA
41 authorization was granted for the clinicians' patients. All patient records that are utilized for research in
42 the state of Minnesota must include research authorization. Records for which the patient has declined
43 authorization were excluded from the study.
44

45 A waiver of informed consent for patients was granted by the IRB as the use of
46 MayoExpertAdvisor was considered to have minimal risk to the patients and to not adversely affect their
47 rights or welfare. Additionally it was deemed that the research could not be practically conducted without
48 waiver of consent as the tools could not run only on select patients for computational efficacy reasons and
49 due to the size of the study. A waiver of HIPAA authorization for patients was granted as: (1) it was
50 deemed there was minimal risk to the privacy of individuals as the data will be de-identified by the IT
51 team before being shared with the research team; (2) the research could not practicably be conducted
52 without the waiver for the reasons stated above; and (3) the research could not be conducted without
53 access to and use of the protected health information, as the MayoExpertAdvisor computing algorithm
54 uses protected health information in its algorithms.
55

56 Results of the study will be disseminated through publication, as well as meetings and newsletters
57 targeted at key stakeholders.
58
59
60

DISCUSSION

Our study will rigorously evaluate the effectiveness of an automated clinical decision support tool for improving adherence to best practices for patients with hyperlipidemia, atrial fibrillation and heart failure. This notification system addresses many of the limitations of previous tools by integrating recommendations seamlessly into the EMR and by providing clinicians with both relevant patient data and actionable recommendations.

This builds on our earlier work in an inpatient setting that used a predecessor of MayoExpertAdvisor²⁶ and illustrates the continued evolution of our clinical decision support system.²⁷ If effective, this decision support tool could be scaled to address the management of other common chronic diseases.

Strengths and Limitations

The strengths of this study are that the clinical decision support tool is integrated within the clinical workflow and was designed with iterative clinician input. The study enrolls primary care clinicians from two specialties (family medicine and internal medicine) and evaluates the impact of the system on three distinct yet common clinical conditions. Further, the study rigorously tests the effectiveness of the tool through a randomized trial using objective and clinically-meaningful endpoints (i.e., changes in care to align with ideal management).

The main weakness of the study is that the findings may lack generalizability as MayoExpertAdvisor is a proprietary system, not yet available to unaffiliated institutions, and it was tested in an academic medical center. Other limitations include our lack of tracking of outcome measures such as ED visits, hospitalizations, or deaths, which during the study timeframe would mainly be to ensure that the implementing MayoExpertAdvisor did not inadvertently lead to unintended negative consequences. We also did not stratify clinicians based on baseline adherence to the guidelines, which could lead to imbalances in the groups at baseline.

Contributorship Statement: RC and MS were involved in the development and validation of the clinical decision support tool. All authors except MS contributed to the study design. All authors are involved in the implementation of the project. MK, REC, and MS wrote the first draft of the manuscript. All other authors revised it critically. All authors gave final approval for publication.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Competing Interests: None.

Data Sharing Statement: No data is available to the study team at this time.

1
2
3
4
5
6
7
8
9
10
11
12
13 **Figure 1: MayoExpertAdvisor (MEA) Alerts**

14
15 **LEGEND**

16 The EMR notifies the clinicians of MEA recommendations in three ways:

- 17 1. In the patient appointment section, MEA is seen with the number of recommendations in parentheses
18 next to the patient's name.
19 2. MEA also appears as a clinical alert.
20 3. Within the EMR banner, there is also a MEA alert that opens the MEA screen.
21
22

23 **Figure 2: MayoExpertAdvisor (MEA) User Interface**

24
25 **LEGEND**

26 A. Care Recommendation

27 Depending on the individual patient's date in the EHR, MEA makes a recommendation.

28 B. Vitals

29 Most recent outpatient vital signs.

30 C. Relevant Patient Data

31 The most relevant demographics, conditions, and lab results for managing the given condition.

32 D. Resources for Next Steps

33 Additional condition-specific tools (e.g. list of moderate and high intensity statins) to assist in
34 recommendations.

35 E. Risk Calculators

36 Condition-specific risk calculators with a patient's data prefilled for real-time calculations.

37 F. Decision Aids

38 Mayo-vetted shared decision-making tools. Field values are prefilled with patient data.
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation* 2016;133(4):e38-360. doi: 10.1161/cir.0000000000000350 [published Online First: 2015/12/18]
2. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Journal of the American College of Cardiology* 2014;64(21):e1-76. doi: 10.1016/j.jacc.2014.03.022 [published Online First: 2014/04/02]
3. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology* 2014;63(25 Pt B):2889-934. doi: 10.1016/j.jacc.2013.11.002 [published Online First: 2013/11/19]
4. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology* 2013;62(16):e147-239. doi: 10.1016/j.jacc.2013.05.019 [published Online First: 2013/06/12]
5. Chan PS, Oetgen WJ, Buchanan D, et al. Cardiac performance measure compliance in outpatients: the American College of Cardiology and National Cardiovascular Data Registry's PINNACLE (Practice Innovation And Clinical Excellence) program. *Journal of the American College of Cardiology* 2010;56(1):8-14. doi: 10.1016/j.jacc.2010.03.043 [published Online First: 2010/07/14]
6. Pencina MJ, Navar-Boggan AM, D'Agostino RB, Sr., et al. Application of new cholesterol guidelines to a population-based sample. *The New England journal of medicine* 2014;370(15):1422-31. doi: 10.1056/NEJMoa1315665 [published Online First: 2014/03/22]
7. Fonarow GC, Yancy CW, Hernandez AF, et al. Potential impact of optimal implementation of evidence-based heart failure therapies on mortality. *American heart journal* 2011;161(6):1024-30.e3. doi: 10.1016/j.ahj.2011.01.027 [published Online First: 2011/06/07]
8. Glazer NL, Dublin S, Smith NL, et al. Newly detected atrial fibrillation and compliance with antithrombotic guidelines. *Archives of internal medicine* 2007;167(3):246-52. doi: 10.1001/archinte.167.3.246 [published Online First: 2007/02/14]
9. Ogilvie IM, Newton N, Welner SA, et al. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *The American journal of medicine* 2010;123(7):638-45.e4. doi: 10.1016/j.amjmed.2009.11.025 [published Online First: 2010/07/09]
10. Nieuwlaat R, Schwalm JD, Khatib R, et al. Why are we failing to implement effective therapies in cardiovascular disease? *European heart journal* 2013;34(17):1262-9. doi: 10.1093/eurheartj/ehs481 [published Online First: 2013/02/05]
11. Njie GJ, Proia KK, Thota AB, et al. Clinical Decision Support Systems and Prevention: A Community Guide Cardiovascular Disease Systematic Review. *American journal of preventive medicine* 2015;49(5):784-95. doi: 10.1016/j.amepre.2015.04.006 [published Online First: 2015/10/20]
12. Bertoni AG, Bonds DE, Chen H, et al. Impact of a multifaceted intervention on cholesterol management in primary care practices: guideline adherence for heart health randomized trial. *Archives of internal medicine* 2009;169(7):678-86. doi: 10.1001/archinternmed.2009.44 [published Online First: 2009/04/15]
13. Fretheim A, Oxman AD, Havelrud K, et al. Rational prescribing in primary care (RaPP): a cluster randomized trial of a tailored intervention. *PLoS medicine* 2006;3(6):e134. doi: 10.1371/journal.pmed.0030134 [published Online First: 2006/06/02]

14. Lester WT, Grant RW, Barnett GO, et al. Randomized controlled trial of an informatics-based intervention to increase statin prescription for secondary prevention of coronary disease. *Journal of general internal medicine* 2006;21(1):22-9. doi: 10.1111/j.1525-1497.2005.00268.x [published Online First: 2006/01/21]
15. Tierney WM, Overhage JM, Murray MD, et al. Effects of computerized guidelines for managing heart disease in primary care. *Journal of general internal medicine* 2003;18(12):967-76. [published Online First: 2003/12/23]
16. Bright TJ, Wong A, Dhurjati R, et al. Effect of clinical decision-support systems: a systematic review. *Annals of internal medicine* 2012;157(1):29-43. doi: 10.7326/0003-4819-157-1-201207030-00450 [published Online First: 2012/07/04]
17. Kawamoto K, Houlihan CA, Balas EA, et al. Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success. *BMJ (Clinical research ed)* 2005;330(7494):765. doi: 10.1136/bmj.38398.500764.8F [published Online First: 2005/03/16]
18. Sittig DF, Wright A, Osheroff JA, et al. Grand challenges in clinical decision support. *Journal of biomedical informatics* 2008;41(2):387-92. doi: 10.1016/j.jbi.2007.09.003 [published Online First: 2007/11/22]
19. Cook DA, Enders F, Linderbaum JA, et al. Speed and accuracy of a point of care web-based knowledge resource for clinicians: a controlled crossover trial. *Interactive journal of medical research* 2014;3(1):e7. doi: 10.2196/ijmr.2811 [published Online First: 2014/02/26]
20. Cook DA, Sorensen KJ, Wilkinson JM, et al. Barriers and decisions when answering clinical questions at the point of care: a grounded theory study. *JAMA internal medicine* 2013;173(21):1962-9. doi: 10.1001/jamainternmed.2013.10103 [published Online First: 2013/08/28]
21. Lopez-Jimenez F, Simha V, Thomas RJ, et al. A summary and critical assessment of the 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: filling the gaps. *Mayo Clinic proceedings* 2014;89(9):1257-78. doi: 10.1016/j.mayocp.2014.06.016 [published Online First: 2014/08/19]
22. Weymiller AJ, Montori VM, Jones LA, et al. Helping patients with type 2 diabetes mellitus make treatment decisions: statin choice randomized trial. *Archives of internal medicine* 2007;167(10):1076-82. doi: 10.1001/archinte.167.10.1076 [published Online First: 2007/05/30]
23. Nielsen J, Molich R. Heuristic evaluation of user interfaces. Proceedings of the SIGCHI Conference on Human Factors in Computing Systems. Seattle, Washington, USA: ACM, 1990:249-56.
24. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010;137(2):263-72. doi: 10.1378/chest.09-1584 [published Online First: 2009/09/19]
25. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;138(5):1093-100. doi: 10.1378/chest.10-0134 [published Online First: 2010/03/20]
26. Cook DA, Enders F, Caraballo PJ, et al. An automated clinical alert system for newly-diagnosed atrial fibrillation. *PloS one* 2015;10(4):e0122153. doi: 10.1371/journal.pone.0122153 [published Online First: 2015/04/08]
27. Cook DA, Sorensen KJ, Hersh W, et al. Features of effective medical knowledge resources to support point of care learning: a focus group study. *PloS one* 2013;8(11):e80318. doi: 10.1371/journal.pone.0080318 [published Online First: 2013/11/28]

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

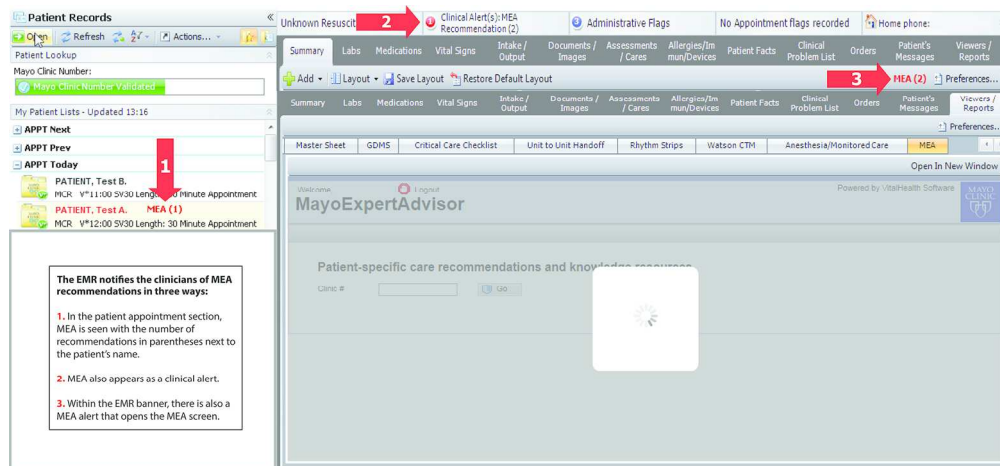


Figure 1

173x81mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

MayoExpertAdvisor Patient-specific care recommendations and knowledge resources.

Patient, Test

Blood Pressure 145/85 mm/Hg 08-Aug-2016 **B**

Heart Rate 58.0 bpm 08-Aug-2016

Weight 95.0 kg 08-Aug-2016

BMI 38.1 08-Aug-2016

Primary Physician Provider, Test

[Refresh data](#)

Feedback

Please help improve this product by providing feedback.

Conditions

Hyperlipidemia

Care Recommendation:

Consider moderate- to high-intensity statin therapy due to LDL ≥ 190 **A**

Relevant Patient Data **C**

Demographics

Adult

Conditions/Problems

Hyperlipidemia

Lab Results

Total cholesterol 289 mg/dL 13-Nov-2014

HDL 73 mg/dL 13-Nov-2014

LDL 200 mg/dL 13-Nov-2014

Non HDL Cholesterol 217 mg/dL 13-Nov-2014

Resources for Next Steps **D**

Moderate- to high-intensity statin dosing and surveillance recommendations

10 Year Risk of Major Cardiac Event (ACC ASCVD): 3.4% **E** [View tool](#)

30 Year Risk of Major Cardiac Event: 25% [View tool](#)

Decision Aids **F**

** Statin Decision Aid **

Ask Mayo Expert

Hyperlipidemia

Patient Education **G**

Hyperlipidemia

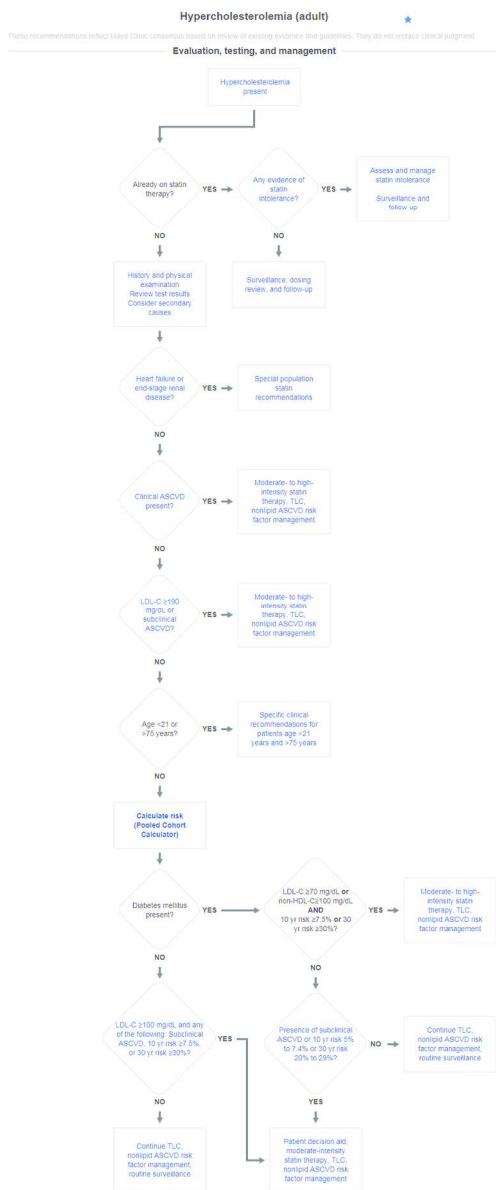
[Hide details and knowledge resources](#)

Figure 2

173x116mm (300 x 300 DPI)

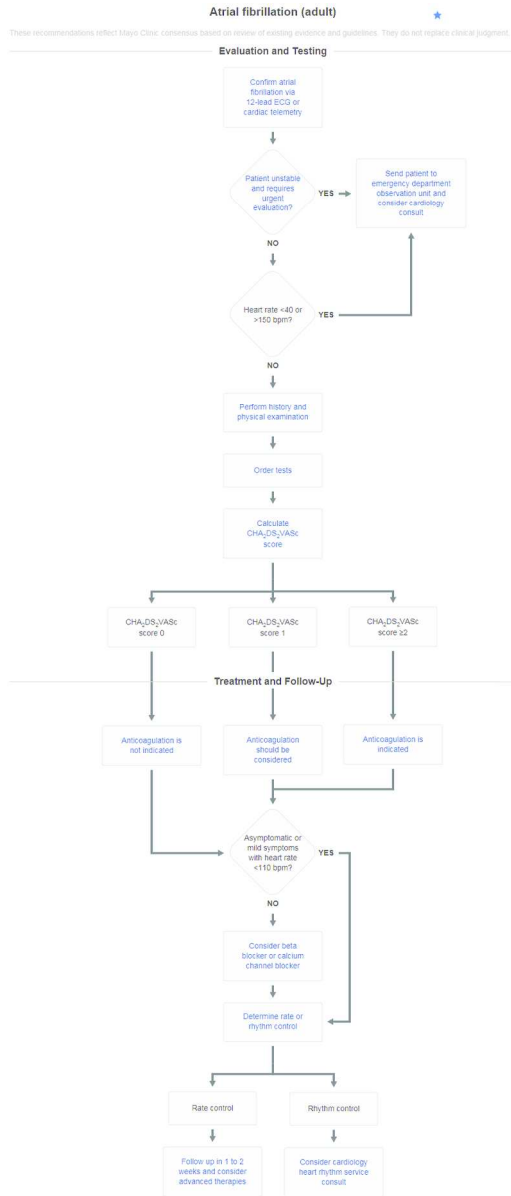
view only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



98x233mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



100x233mm (300 x 300 DPI)

