Mass General Brigham

Detailed Study Protocol:

Electronic Alert-Based Computerized Decision Support to Improve Testing For Primary Aldosteronism in Patients with Hypertension (ALERT-PA)

NCT05925569

Protocol Version Date: 01 November 2024

Institutional Review Board
Intervention/Interaction Detailed Protocol

Principal Investigator: Jenifer M. Brown, MD

Project Title: Electronic Alert-Based Computerized Decision Support to Improve Testing For Primary Aldosteronism in Patients with Hypertension (ALERT-PA)

Version Date: 1 November 2024

Version Name/Number: Version 3.0

1. Background and Significance

Primary aldosteronism (PA) is a syndrome of autonomous aldosterone production by the adrenal glands, in which aldosterone is produced despite volume expansion, hypertension, and suppression of its upstream regulators: renin and angiotensin II[1].

In PA, chronic activation of the mineralocorticoid receptor (MR) in the kidneys, vasculature, heart, and other tissues results in not only fluid retention and hypertension but also excess risk of cardiovascular, metabolic, and renal outcomes. Even compared to essential hypertension, PA is associated with elevated rates of atrial fibrillation, heart failure, coronary artery disease, stroke, chronic kidney disease, diabetes, and death[2,3]. These adverse consequences can be mitigated by targeted treatment of PA with existing MR antagonists or adrenalectomy, when indicated[4], but patients first have to be identified to benefit from these therapies.

The most common secondary cause of hypertension, PA is highly prevalent across the hypertensive spectrum, accounting for 10-25% of cases, and is further enriched in high-risk populations such as those with severe or resistant hypertension and those with hypertension plus hypokalemia[5,6].

Current clinical guidelines from the American College of Cardiology/American Heart Association, Endocrine Society, and others recommend screening for PA in a defined set of high-risk populations[7-9]:

1. resistant hypertension
2. severe hypertension (>150/100mmHg on three measurements)
3. hypertension accompanied by spontaneous or diuretic-induced hypokalemia
4. hypertension and the presence of an adrenal mass
5. hypertension with atrial fibrillation
6. hypertension with sleep apnea
7. family history of early onset hypertension, early stroke, or PA.

However, evidence across multiple academic medical centers, the Veterans Administration healthcare system, and sites in the U.S., Canada, and elsewhere have demonstrated consistently abysmal rates of

compliance with recommended screening. Of guideline-eligible patients, <5% are screened for PA, including within primary care as well as in endocrinology, nephrology, and cardiology subspecialty practices[10-15]. When patients are screened, they are more likely to be treated with MR antagonists and to achieve better blood pressure control. However, the vast majority of patients with PA, who are at elevated risk for cardiometabolic morbidity and mortality, are never identified or treated with established targeted therapies.

Prior studies have demonstrated that an alert-based clinical decision support (CDS) tool can improve adherence to clinical guidelines and in some instances, improve clinical outcomes[16,17]. Screening for PA is well-suited for an alert-based CDS tool because there is established evidence of low clinician awareness and adherence to existing clinical practice guidelines, and there is an effective methodology for screening based on simple phlebotomy (measurement of plasma renin activity, aldosterone, and basic metabolic panel). If this strategy is successful at improving rates of PA screening and management, it could be easily scaled up to reach patients more broadly across U.S. medical centers.

Summary: PA is a common but rarely recognized disorder that causes excess cardiovascular and renal risk and has approved, targeted, risk-mitigating treatments. Raising awareness of this condition, alerting clinicians to the presence of guideline-indications for screening, and streamlining the process of testing for PA will be crucial to improving recognition and management of this important condition. This study aims to study the impact of an alert-based CDS tool using an embedded Best Practice Advisory (BPA) within the Epic electronic medical record on rates of screening for PA, referral to specialist PA care, treatment with MR antagonists, and PA diagnosis.

2. Specific Aims and Objectives

The central objective of this study is to quantify the impact of an alert-based CDS tool within EPIC on rates of screening for primary aldosteronism within patients meeting current clinical guideline recommendations.

Aim #1: To determine the impact of the BPA, using the EPIC Electronic Health Record (EHR) CDS software, on the 6-month frequency of aldosterone and renin testing in patients who meet clinical guidelines for screening for PA and are not currently diagnosed with PA or treated with MR antagonists. We hypothesize that alert-based CDS will increase the frequency of screening labs by 2-fold in patients meeting clinical guidelines criteria for screening.

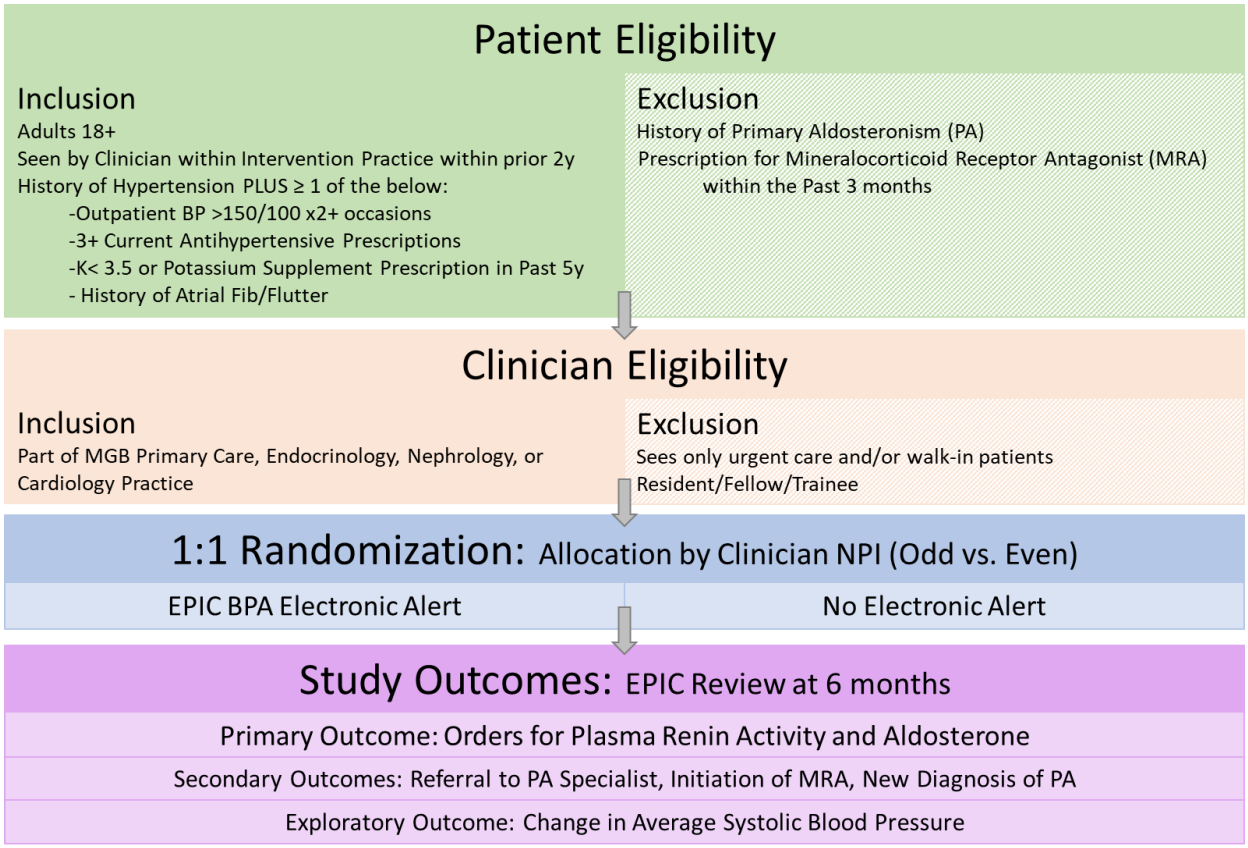
Aim #2: To determine the impact of the EPIC BPA on the frequency of a PA-related referral, an MRA prescription, or a new ICD diagnosis of PA, secondary hypertension, or endocrine hypertension in high-risk patients.

Exploratory Aim #3: To determine the impact of the EPIC BPA on the change in systolic blood pressure, as determined by the average of the three most recent outpatient readings at the end of the study period compared to the average of the three last outpatient readings prior to launch of the BPA.

3. General Description of Study Design

The study protocol is a single-center Quality Improvement initiative performed as a cluster-randomized controlled trial designed to evaluate the impact of a Best Practice Advisory (BPA) on rates of screening for PA in guideline-eligible patients. Patients meeting inclusion/exclusion criteria will comprise the study population, with randomization occurring at the level of their treating clinician (Attending Physician, Nurse Practitioner, or Physician Assistant) to minimize spillover/contamination effects of the BPA onto other patients treated by the same clinician. Treating clinicians within primary care and relevant specialties including endocrinology, nephrology, and cardiology will be randomized 1:1 to receive or not receive a BPA prompting screening for PA with laboratory testing of plasma aldosterone, plasma renin activity, and a basic metabolic panel, as well as an order for an e-consult to provide guidance on interpretation of results, for eligible patients. Outcomes will be ascertained by EPIC EHR review at 6 months.

Figure 1. Study Schema.



4. Subject Selection

Sample Size: We will aim to enroll adult patients with hypertension meeting the below inclusion/exclusion criteria during the 12-week study enrollment period.

Study Population
Eligible patients will meet the following enrollment criteria:
Inclusion

- Adults 18+
- Seen by clinician at one of the intervention practices at least once in the prior 2 years
- History of Hypertension (ICD Code) PLUS ≥1 of the below:
    - Outpatient BP >150/100 on 2 or more occasions
    - 3+ Current antihypertensive medication prescriptions
    - Potassium level <3.5 or Potassium supplement prescription in the last 5 years
    - History of Atrial Fibrillation or Atrial Flutter (ICD Code)

Exclusion:

- History of Primary Aldosteronism (ICD Code)
- Prescription for a Mineralocorticoid Receptor Antagonist (MRA) within the last 3 months

Clinicians who will undergo randomization will meet the following enrollment criteria*:*

Inclusion

- Practitioner within MGB-affiliated clinics in Primary Care or in one of the Cardiology, Endocrinology, or Nephrology Medical Specialties Clinics

Exclusion

- Clinicians who only see urgent care and/or walk-in patients.
- Residents/Fellows/Trainees

Recruitment Methods

Eligible patients will be identified using an EPIC EHR query built through collaboration with the BWH Digital Health Innovation Group (DHIG) as outlined below. Each treating clinician meeting the above inclusion/exclusion criteria will be randomly assigned in a 1:1 ratio to the BPA intervention group ("alert group") or to the control ("no alert group") according to their National Provider Identifier (NPI) number (odd vs even). NPI number was selected because this has been used successfully in prior alert-based CDS trials within MGB in the past[17] and can help to reduce the odds that a provider applies information from one patient's BPA alert to the care of another patient, potentially violating the randomization and contaminating the study results.

5. Subject Enrollment

Subject Informed Consent

Because this trial is a Quality Improvement initiative and all patients being identified for PA screening meet current clinical guideline indications for testing, we have applied for a Waiver of Informed Consent, as has been granted in previous similar BPA-based Quality Improvement trials at MGB[17]. This trial is a comparative study of clinician behavior with vs. without an electronic alert. As a result, signing of Informed Consent would tip off the provider about the ongoing Quality Improvement initiative and could influence the screening of patients for PA. This could bias patient and/or provider behavior, and thus could confound the trial results by diminishing the apparent impact of the alert.

Similarly, an important consideration in the study design is whether an announcement should be made before the start of the trial to notify clinicians about the alert-based CDS. An announcement of the

randomized controlled trial of alert-based CDS to increase guideline-adherence to PA screening for guideline-eligible patients with hypertension could result in increased awareness of the need for screening among all providers, including those ultimately randomized to the control group with no BPA alert, and thus could bias the study toward the null and underestimate the impact of the randomized study intervention.

6. STUDY PROCEDURES

Determination of Study Eligibility

The BPA will identify eligible patients within EPIC using the EHR medical history, visit diagnoses, problem list, laboratory results, medication prescriptions, and vital signs to identify adult patients seen in one of the intervention practices within the last 2 years who carries a diagnosis of hypertension and one or more of the PA risk factors (outpatient BP >150/100 on 2 or more occasions, 3+ current antihypertensive medication prescriptions, a potassium level <3.5 or potassium supplement prescription in the last 5 years, and/or history of Atrial Fibrillation or Atrial Flutter). Patients with a history of primary aldosteronism, as ascertained using the same EHR data as above, will be excluded given they do not require repeat screening. Similarly, patients with an active or recent prescription for an MRA (spironolactone, eplerenone, finerenone) within the last 3 months will be excluded given that 1) these prescriptions can substantially impact the screening test interpretation, 2) these medications may be prescribed due to a clinical impression of PA even in the absence of a diagnostic code, and 3) MRA prescription is one of the outcome measures.

Clinicians will be identified based on a list of providers who see patients within the MGB primary care, cardiovascular medicine, nephrology, and endocrinology clinics. Providers who see only urgent care and/or walk-in patients will be excluded, as routine PA screening in guideline-eligible patients would not typically be recommended in this clinical context. Trainees will be excluded as they may practice under the supervision of multiple Attending Physicians and can thus represent a source of contamination between the intervention and control groups.

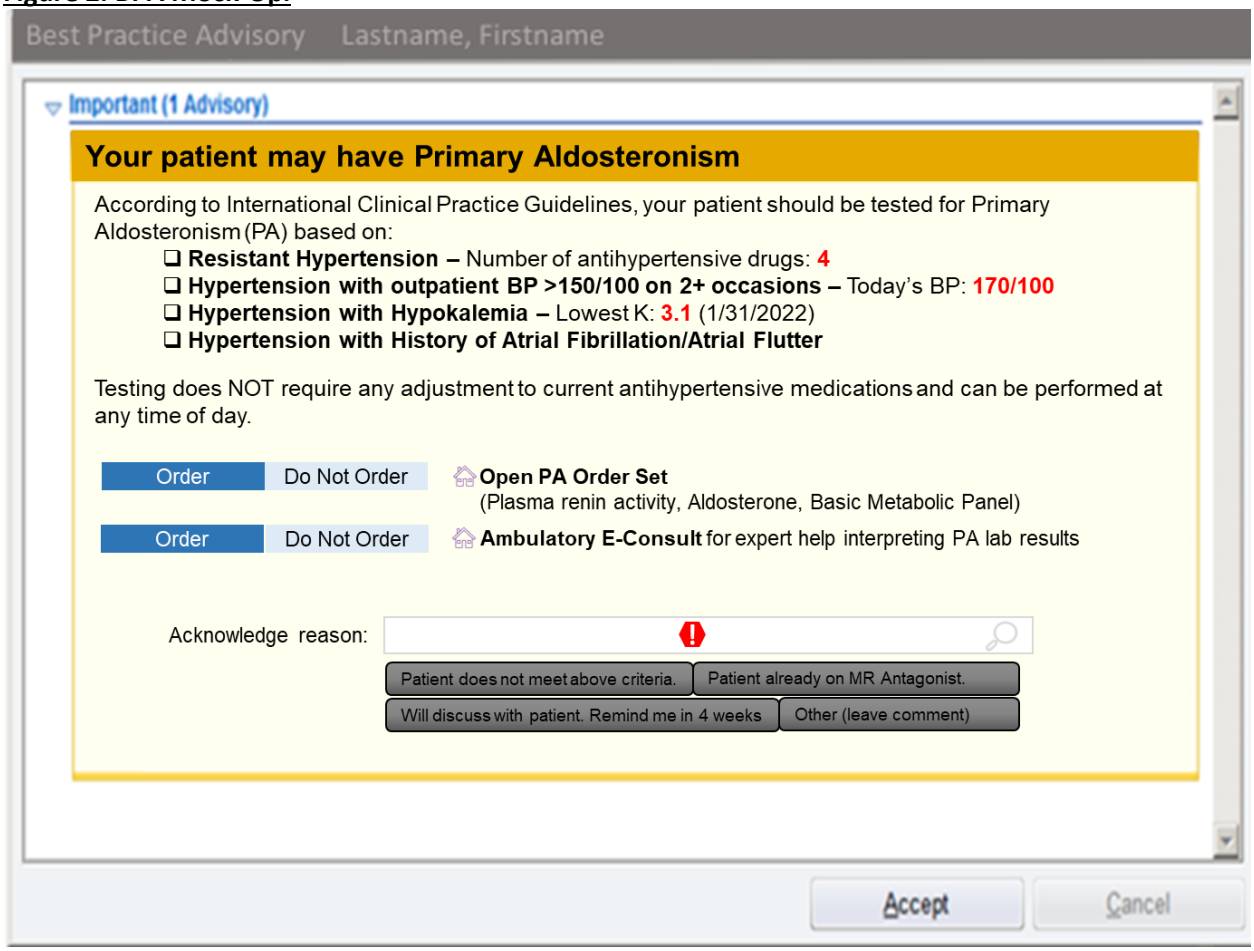
Study Group Assignment

Each patient meeting study inclusion/exclusion criteria will be randomly assigned to the BPA alert intervention group or the no alert control group according to the treating clinician of record's NPI number. Study enrollment will be considered to start at the time of the patient's first attended clinic visit with their treating clinician. For patients with multiple eligible clinicians (e.g. a PCP and one or more specialists), only one clinician per patient will be assigned to receive or not receive alerts.

BPA Intervention

For patients randomly assigned to the BPA Alert Group, an on-screen electronic alert (Figure 2 below) will be issued during the outpatient clinical encounter than notifies the clinician that their patient should be screened for PA. The clinician will be provided with on-screen details of which patient-specific risk factors qualified them for PA screening and with an option to order a plasma renin activity, aldosterone, and basic metabolic panel. The clinician will also receive an option to order an eConsult for expert guidance on interpretation of the test results. If the clinician does not order the PA screening labs, they will be able to continue with clinical EHR documentation but will need to select a reason they opted not to follow the alert's evidence-based clinical practice recommendation.

Figure 2. BPA Mock-Up.



For patients assigned to the BPA Alert Group, the BPA intervention will appear within each outpatient encounter with their clinician until the PA screening labs are ordered, or if never ordered, then for the duration of the study period. In-person and virtual appointments will be considered equivalent for the purposes of study group assignment and for BPA alert firing, in the case of the intervention group.

Data Collection and Ascertainment of Outcomes

Follow-up will be performed and outcomes ascertained at 6 months from study enrollment by review of the EPIC EHR, including review of order entry, ICD diagnostic codes, laboratory results, outpatient blood pressure values, notes, and the Care Everywhere section. Similar comprehensive EPIC EHR review will be performed up to 5 years following study completion to enhance the robustness of the de-identified research registry and facilitate ascertainment of longer-term study outcomes including long-term blood pressure control, antihypertensive medication use, and clinical events, in this cohort with hypertension and clinical indications for primary aldosteronism screening.

Primary Outcomes:

- Frequency of aldosterone/renin laboratory testing orders by provider

Secondary Outcomes:

- Frequency of PA-related Specialty Referral (endocrine, cardiology)
- Frequency of Empiric MRA Prescription (spironolactone, eplerenone, finerenone)

- Frequency of new ICD Diagnostic Code for PA, Secondary Hypertension, or Endocrine Hypertension
- Frequency of E-Consult order by provider
- Frequency of a "Positive" screening test result suggestive of PA among patients who are screened

Exploratory Outcome:

- Change in systolic blood pressure (difference between average of last 3 outpatient readings prior to study initiation vs. average of first 3 outpatient readings after study completion)
- Blood pressure control and clinical events up to 5y after study enrollment to determine term natural history (in the control group) and impact of the alert (in active BPA alert group) over medium-term

Compensation

There will be no patient or provider renumeration provided for this Quality Improvement clinical trial protocol.

Data Sharing

No patient- or provider-level data will be shared outside of the institution.

Study Timeline

We project a 3-month start-up time including design, programming, and troubleshooting of the EPIC BPA. Study patient enrollment will occur over a 12-week study enrollment period. Final follow-up data for the primary and secondary study outcomes will be collected 6 months after the last patient is randomized.

7. Risks and Discomforts

This Quality Improvement study yields minimal risk to patients and clinicians because it consists only of an electronic alert to the clinician regarding the guideline recommendation to screen for PA. The electronic alert does not mandate prescription of any medications or other therapeutic interventions. The clinician is able to use their own clinical judgement and best clinical practice to guide their selection among the options to order labs for aldosterone and renin activity, to order an E-Consult for expert guidance on interpretation of results, or to provide a reason for declining. Because only a small minority of patients are currently receiving indicated screening for PA under the current status quo, patients in the control group are not exposed to any notable excess risk. The risk to patients in the Alert Group is only that risk inherent in receiving clinical guidance from their healthcare provider to undergo indicated laboratory testing, which has the potential to include results that can cause anxiety or distress to the patient. The risk to the provider is also minimal because the alert is limited to notification regarding evidence-based clinical practice recommendations for PA screening.

Participant and clinical confidentiality is critical. For data analysis, all participant records will be labeled with a study code that bears no resemblance to their name or identifiers. All participant records and specimens will be labeled with this code as to de-identify their participation. Subject information will be

kept in de-identified databases stored on a secure MGB computer and RedCAP and accessible only to the study team. Identifiable information will not be shared.

8. Benefits

PA is a common but rarely recognized disorder that causes excess cardiovascular and renal risk and has approved, targeted, risk-mitigating treatments. Raising awareness of this condition, alerting clinicians to the presence of guideline-indications for screening, and streamlining the process of testing for PA will be crucial to improving recognition of this important condition. Patients who are assigned to the Alert may be more likely to receive clinically indicated screening that results in changes to their clinical management, which ultimately improves their health. If this intervention is found to be successful in improving rates of adherence to clinical practice guidelines, it could be feasibly scaled up to reach patients and clinicians across local, regional, and national healthcare settings in which EPIC is employed.

9. Statistical Analysis

Analysis Plan

The primary statistical analysis will be to compare the frequency of ordering of PA screening laboratory tests for patients meeting clinical guideline recommendations in those patients whose clinicians receive an electronic BPA alert vs. usual care (no alert). The secondary analyses will compare the frequency of PA-related specialty referral, MRA initiation, and a new diagnosis of PA. Descriptive analyses will report the frequency with which an e-consult for expert guidance on interpretation of results is ordered and will report the frequency of positive screening results suggestive of PA among those patients who are screened. The proposed study is not powered to show a difference in blood pressure control, but an exploratory analysis will compare the change in average systolic blood pressure during the study period between the intervention (alert) and control (no alert) groups.

Sample Size and Power

Based on prior randomized controlled trials of alert-based CDS tools[16,17], we conservatively estimate that the BPA notification will increase screening for PA by 2-fold in patients meeting guideline-based criteria. Assuming a baseline rate of screening of approximately 4%[10-15], we estimate that we will need 800 patients in each group (total sample of 1600) to detect a 2-fold increase in the rate of screening with 80% power at a two-sided alpha of 0.05, assuming approximately 4 patients per cluster and an intraclass correlation coefficient of 0.1.

However, based on early pilot testing of the study CDS alert running in Epic shadow mode, we discovered that the initially proposed sample size of 1600 would accrue too quickly, with approximately 200 potentially eligible patients per day resulting in only an 8-day study enrollment period. Given there is no additional risk to patients or clinicians by expanding the sample size, we will instead continue enrollment for a fixed 12-week duration to maximize study validity, with the final sample size dependent on the number of patients who ultimately meet eligibility criteria and present for qualifying clinical appointments with eligible providers over the 12-week enrollment period.

10. Monitoring and Quality Assurance

Data, in the form of pertinent medical history (medical diagnoses, laboratory results, medication prescriptions, referral orders, and vital signs) will be collected during the study. All of the collected material will be used solely for research purposes. Data will be collected from the EPIC EHR through the process built to deliver the BPA and ascertain outcomes and will be stored in RedCAP. Only the PI and research study staff have access to these data. The database where all the data is entered will have no identifiers that would allow someone to identify a subject. The database will comply with both IRB and HIPPA regulations.

Prior to any participant enrollment, the protocol will be reviewed and approved by the Human Research Committee. In accordance with their requirements, an annual review of the study will be submitted to maintain ongoing approval to conduct the research. Any and all adverse events will be reported to the Human Research Committee on a timeline based on the severity. Life-threatening conditions, whether or not they are thought to be related to the study, will be reported immediately.

Data will be reviewed for validity and accuracy by the principal investigator, and the principal investigator will be responsible for strict adherence to the IRB-approved protocol. They will be responsible for reviewing the safety and/or efficacy data and determining whether the research should be altered or stopped. If necessary, any proposed changes will require a protocol amendment to be submitted to the IRB. Any deviations from the protocol must be explained and documented by the investigator.

11. Privacy and Confidentiality

- ☒ Study procedures will be conducted in a private setting
- ☒ Only data and/or specimens necessary for the conduct of the study will be collected
- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- ☒ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
- ☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research

☐ Additional privacy and/or confidentiality protections

12. References

1. Vaidya A, Hundemer GL, Nanba K, Parksook WW, Brown JM. Primary Aldosteronism: State-of-the-Art Review. *Am J Hypertens*. 2022;35:967-988. doi: 10.1093/ajh/hpac079
2. Monticone S, D'Ascenzo F, Moretti C, Williams TA, Veglio F, Gaita F, Mulatero P. Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: a systematic review and meta-analysis. *The Lancet Diabetes & Endocrinology*. 2018;6:41-50. doi: 10.1016/S2213-8587(17)30319-4
3. Monticone S, Sconfienza E, D'Ascenzo F, Buffolo F, Satoh F, Sechi LA, Veglio F, Mulatero P. Renal damage in primary aldosteronism: a systematic review and meta-analysis. *J Hypertens*. 2020;38:3-12. doi: 10.1097/HJH.0000000000002216
4. Hundemer GL, Curhan GC, Yozamp N, Wang M, Vaidya A. Incidence of Atrial Fibrillation and Mineralocorticoid Receptor Activity in Patients With Medically and Surgically Treated Primary Aldosteronism. *JAMA Cardiology*. 2018;3:768-774.
5. Brown JM, Siddiqui M, Calhoun DA, Carey RM, Hopkins PN, Williams GH, Vaidya A. The Unrecognized Prevalence of Primary Aldosteronism: A Cross-Sectional Study. *Annals of Internal Medicine*. 2020;173:10-20. doi: 10.7326/M20-0065
6. Burrello J, Monticone S, Losano I, Cavaglia G, Buffolo F, Tetti M, Covella M, Rabbia F, Veglio F, Pasini B, et al. Prevalence of hypokalemia and primary aldosteronism in 5100 patients referred to a tertiary hypertension unit. *Hypertension*. 2020:epub-epub. doi: 10.1161/HYPERTENSIONAHA.119.14063
7. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task F. *Circulation*. 2018;138:e426-e483. doi: 10.1161/CIR.0000000000000597
8. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, Stowasser M, Young WF. The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*. 2016;101:1889-1916. doi: 10.1210/jc.2015-4061
9. Rossi GP, Bisogni V, Bacca AV, Belfiore A, Cesari M, Concistre A, Del Pinto R, Fabris B, Fallo F, Fava C, et al. The 2020 Italian Society of Arterial Hypertension (SIIA) practical guidelines for the management of primary aldosteronism. *Int J Cardiol Hypertens*. 2020;5:100029. doi: 10.1016/j.ijchy.2020.100029
10. Cohen JB, Cohen DL, Herman DS, Leppert JT, Byrd JB, Bhalla V. Testing for Primary Aldosteronism and Mineralocorticoid Receptor Antagonist Use Among U.S. Veterans. *Annals of Internal Medicine*. 2021;174:289-297. doi: 10.7326/M20-4873
11. Hundemer GL, Imsirovic H, Vaidya A, Yozamp N, Goupil R, Madore F, Agharazii M, Knoll G, Sood MM. Screening Rates for Primary Aldosteronism Among Individuals With Hypertension Plus Hypokalemia: A Population-Based Retrospective Cohort Study. *Hypertension*. 2022;79:178-186. doi: 10.1161/HYPERTENSIONAHA.121.18118

12. Jaffe G, Gray Z, Krishnan G, Stedman M, Zheng Y, Han J, Chertow GM, Leppert JT, Bhalla V. Screening Rates for Primary Aldosteronism in Resistant Hypertension: A Cohort Study. *Hypertension*. 2020;75:650-659. doi: 10.1161/HYPERTENSIONAHA.119.14359
13. Turcu AF, Nhan W, Grigoryan S, Zhang L, Urban C, Liu H, Holevinski L, Zhao L. Primary Aldosteronism Screening Rates Differ with Sex, Race, and Comorbidities. *J Am Heart Assoc*. 2022;11:e025952. doi: 10.1161/JAHA.122.025952
14. Ruhle BC, White MG, Alsafran S, Kaplan EL, Angelos P, Grogan RH. Keeping primary aldosteronism in mind: Deficiencies in screening at-risk hypertensives. *Surgery*. 2019;165:221-227. doi: 10.1016/j.surg.2018.05.085
15. Liu Y-y, King J, Kline GA, Padwal RS, Pasieka JL, Chen G, So B, Harvey A, Chin A, Leung AA. Outcomes of a Specialized Clinic on Rates of Investigation and Treatment of Primary Aldosteronism. *JAMA Surgery*. 2021;156:541-541. doi: 10.1001/jamasurg.2021.0254
16. Kucher N, Koo S, Quiroz R, Cooper JM, Paterno MD, Soukonnikov B, Goldhaber SZ. Electronic Alerts to Prevent Venous Thromboembolism among Hospitalized Patients. *New England Journal of Medicine*. 2005;352:969-977.
17. Piazza G, Hurwitz S, Galvin CE, Harrigan L, Baklla S, Hohlfelder B, Carroll B, Landman AB, Emani S, Goldhaber SZ. Alert-based computerized decision support for high-risk hospitalized patients with atrial fibrillation not prescribed anticoagulation: a randomized, controlled trial (AF-ALERT). *Eur Heart J*. 2020;41:1086-1096. doi: 10.1093/eurheartj/ehz385