Improving Recognition and Management of Hypertension in Youth: Comparing Approaches for Extending Effective CDS for use in a Large Rural Health System

IRB Protocol Version: v1.8

IRB Study Acronym: Peds & TeenBP

National Clinical Trial (NCT) Identified Number: 05126082

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1 PROTOCOL SUMMARY

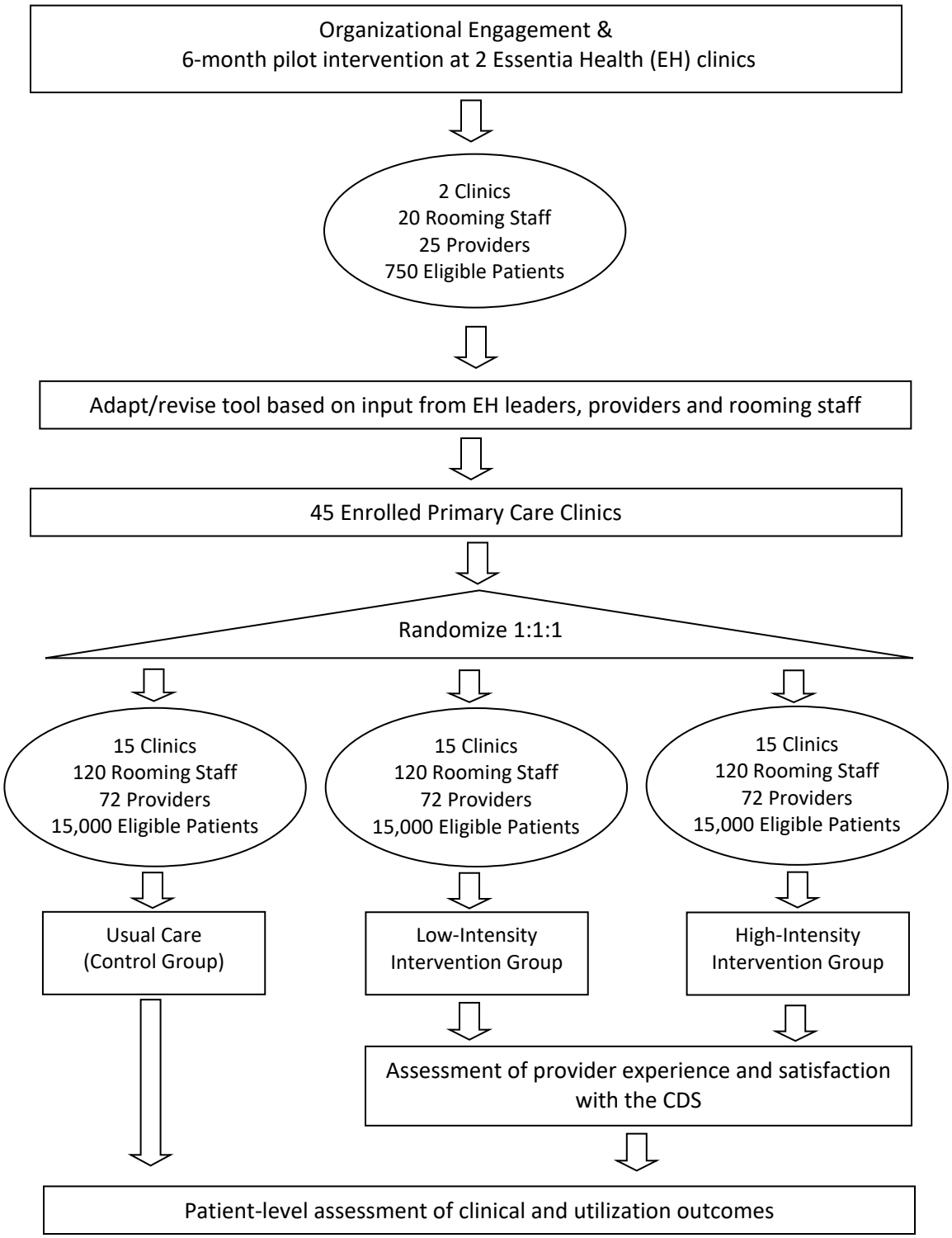
1.1 SYNOPSIS

Title:	Improving Recognition and Management of Hypertension in Youth: Comparing Approaches for Extending Effective CDS for use in a Large Rural Health System
Grant Number:	AHRQ 1R18HS027402-01A1
Study Description:	This research project will adapt the PedsBP clinical decision support (CDS) tool for use at Essentia Health and measure the implementation processes and outcomes. This minimal risk, pragmatic trial will randomize up to 45 Essentia clinics in a 3-arm, cluster-randomized trial. Clinics will be randomly allocated in a 1:1:1 allocation ratio to usual care, low-intensity implementation, or high-intensity implementation of the PedsBP CDS. Study-eligible patients will be allocated to the study arm assigned to the clinic at which the patient has an index visit when blood pressure (BP) is measured. Clinic providers and rooming staff will be interviewed and surveyed to assess experience and satisfaction with the CDS.
Objectives:	Identify optimal intervention implementation strategies for the PedsBP CDS tool. Post-implementation comparisons of high- plus low-intensity implementation versus usual care and high- versus low-intensity implementation will be conducted for the primary endpoints of BP remeasurement at the index visit (for patients with an elevated first BP), and BP recognition within 6 months of the index visit (for patients newly meeting HTN criteria).
Endpoints:	There are two primary outcomes. One is repeat BP measurement during the same clinic visit, of an initial BP that is ≥95th percentile for children 6-12 years or ≥130/80 mmHg for adolescents 13-17 years. Repeat BPs can be measured by providers or rooming staff but will only contribute to this outcome if recorded in the vitals section of the EHR. The other primary outcome is clinical recognition of HTN within 6 months of meeting criteria for HTN. Clinical recognition will include a new diagnosis of HTN (ICD-10: I10) or elevated BP (ICD-10: R03), adding HTN or elevated BP to the problem list. Secondary outcomes will describe management within 6 months of meeting criteria for HTN including: lifestyle counseling, dietitian referrals, subspecialty referrals, initiation of antihypertensive medications and receipt of diagnostic imaging (echocardiogram or renal ultrasound). BP control at 12 months following the index date meeting criteria for HTN will be an exploratory outcome.
Study Population:	To participate in this study, primary care providers must practice at one of the participating EH clinics and meet these additional eligibility criteria: (a) be a pediatric or family medicine care provider (pediatrician, family physician, nurse practitioner or physician assistant), and (b) provide ongoing clinical care for children and adolescents. Patients enrolled will be 6-17 years with BP, height and weight recorded. We estimate patients will have an average of 2.02 visits per patient over the study period. Similar to demographics of the region, the population is 90% white, non-Hispanic.

Description of Sites/Facilities Enrolling Participants:	Pilot - Two Essentia Health primary care clinics CDS control & intervention - up to 45 Essentia Health primary care clinics
Description of Study Intervention/Experimental Manipulation:	Up to 45 community-based, Essentia Health primary care clinics with the largest number of visits among youth 6-17 years will be balanced and randomly allocated in a 1:1:1 allocation ratio to usual care, low-intensity implementation, or high-intensity implementation of the PedsBP CDS.
Study Duration:	Pilot testing and interviews: January 2022 – June 2022 18-month CDS intervention period: August 2022 – January 2024 (*anticipated*) 12-month CDS follow-up period: February 2024 – January 2025 Survey clinicians and rooming: October 2023 – December 2023
Participant Duration:	Pilot interviews of clinicians and staff – April 2022 – June 2022 Data collection for study-eligible adolescent patients – August 1, 2022 – July 31, 2025 Surveys of clinicians and staff – October 2023 – December 2023

1.2 SCHEMA

Cluster Randomized Trial Implementation Process and Design*



* Clinic, staff, provider and patient enrollment numbers are estimated.

1.3 SCHEDULE OF ACTIVITIES

IRB Submission-Related Activities

Phase 1 Study Aspect	Estimated Start Date	Completion Date	Recruitment / Authorization	Consent / Assent	IRB Submission for Approval
Development, quality assurance and testing of the CDS	July 2021	End of Study	Full waiver of HIPAA authorization	Requesting waiver of consent and assent	Submitted initial submission 10/12/20 and amendment 04/28/21
Pilot clinics - PedsBP CDS implementation, operation, quality assurance and testing (see section 9.1.4)	Jan 2022	End of Study	Full waiver of HIPAA authorization	Requesting waiver of consent and assent	Submitted amendment 01/07/22
Interview pilot clinicians and rooming staff	Jan 2022	June 2022	Contact by mail, email or in-person	Informed consent	Submitted amendment 03/16/22
Phase 2 Study Aspect	**Estimated Start**	**Completion Date**	**Recruitment / Authorization**	**Consent / Assent**	**IRB Submission for Approval**
Intervention - CDS implementation, operation, testing and data collection in up to 45 study clinics	Aug 2022	Jan 2025	Full waiver of HIPAA authorization	Requesting waiver of consent and assent	Submitted amendment 08/16/22
Post-Implementation rooming staff and PCP surveys	Oct 2023	Dec 2023	Contact by mail/email	Requesting waiver of informed consent documentation	Submitted amendment 10/09/23

2 INTRODUCTION

2.1 STUDY RATIONALE

Hypertension (HTN) in youth tracks into adulthood, contributing to adult cardiovascular morbidity and mortality. National guidelines for the diagnosis and treatment of HTN in children and adolescents were last updated in 2017, with definitions for HTN that vary by age. To date, most children and adolescents with elevated blood pressure (BP) or HTN are not diagnosed or inadequately treated. Factors that contribute to these deficits in care include: the need to translate pediatric BP measures into BP percentiles, lack of clinician familiarity with pediatric HTN guidelines, and competing demands at clinical encounters.

Electronic health record (EHR)-linked clinical decision support (CDS) can be used to address these barriers and improve the identification and management of elevated BP and HTN in children and adolescents. With funding from NHLBI, our team developed, implemented, and evaluated a sophisticated web-based, EHR-linked CDS to provide patient-specific clinical care recommendations in real time and in accordance with national guidelines for BP management in youth. In a 2-year cluster randomized trial in 20 urban and suburban primary care clinics in an integrated health system in Minnesota, we demonstrated that our CDS increased repeat measurement of elevated BP during a visit and more than doubled clinician recognition of HTN, while promoting dietitian referrals and additional next steps in care consistent with national guidelines. The CDS system was well accepted by providers and as such, is now standard of care in 55 primary care and 17 subspecialty clinics serving children across the HealthPartners health system. Implementation of this CDS, now referred to as PedsBP, in a new health system will help describe the optimal strategies for adaptation and implementation of CDS in clinics serving rural populations.

If the interventions significantly improve identification or management of BP in adolescent study subjects, risks of certain clinical events related to elevated BP (stroke, renal failure, myocardial infarction) may be reduced later in life. If the interventions fail to significantly improve identification or management of BP in adolescent study subjects, that knowledge will also be important because it will direct the attention of investigators to other, potentially more fruitful, lines of investigation. In addition, data comparing low-intensity and high-intensity approaches to CDS implementation will be of interest to health services researches, medical groups and health systems. Thus, regardless of specific findings, the results of this trial will provide important new knowledge that will ultimately contribute to improved care for adolescents with elevated BP.

2.2 BACKGROUND

National guidelines for diagnosing and treating HTN in children and adolescents were published in 2004 as the Fourth Report[36] and were updated in 2017, as the Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents (2017 Guideline).[9] The 2017 Guideline defines HTN in children 12 and younger, as blood pressure (BP) at 3 separate visits at or above the 95th percentile, and for adolescents 13 to 17 years, BP at 3 separate visits at or above 130/80 mmHg. Stage 2 HTN is defined as 3 or more BP measurements at or above 95th percentile + 12 mmHg or 140/90 mmHg. Elevated BP, previously known as pre-hypertension, includes patients with one or more BP measurements at or above the 90th percentile or 120/80 mmHg, but not meeting criteria for HTN.

The prevalence of HTN can be estimated from clinical or population-based samples. Using definitions from the 2004 Fourth Report, of 14,187 children and adolescents with at least three preventive health visits to a single Midwestern health system from 1999 to 2006, 3.4% met criteria for elevated BP and 3.6% met criteria for HTN.[37] In contrast, a school-based screening of nearly 7,000 adolescents, conducted from 2003 to 2005, reported elevated BP in 15.7% and

HTN in 3.2% (2.6% stage 1 and 0.6% stage 2).[13] A large retrospective cohort study using data from 196 ambulatory clinics within a large practice-based research network found that of children and adolescents with visits from 1999-2014, 10.1% had elevated BP and 3.3% met criteria for HTN.[12] Using the 2017 Guideline definitions, the prevalence of HTN in children and adolescents has ranged from 3 to 5%.[14,15,38]

Elevated BP and HTN during adolescence, although generally asymptomatic, is associated with immediate and long-term adverse health effects, including left ventricular hypertrophy (LVH) and carotid intima-media thickness.[39] The effects of BP on target organs are graded, with the risk for developing LVH increasing progressively with increases in BP.[39-41] Studies have shown that over 20% of adolescents with HTN have concurrent evidence of LVH.[40,42,43] Obesity is associated with elevated BP[13,44-46] and is an independent risk for cardiovascular disease.[47] Elevated BP during childhood and adolescence is associated with adult HTN and predicts long-term cardiovascular morbidity and mortality.[48-51] In a study of Swedish males, elevated diastolic BP (DBP) during late adolescence was associated with a 10% to 15% increase in all-cause mortality over a median of 24 years of follow up.[4]

For biological, behavioral, and pragmatic reasons, late childhood through adolescence is an ideal period for identifying and treating HTN. First, compared to younger children, BPs in older children and adolescents are more highly correlated with adult BPs.[50,52,53] In addition, incident HTN in this age group is usually essential, and does not require extensive testing for secondary causes.[9] Third, unlike younger children, older children and adolescents have increased autonomy and may be better able to make healthy choices regarding diet and exercise. Identifying school-aged children and adolescents with HTN and providing targeted education and recommendations for exercise and nutrition could have lifelong benefits. Finally, older children and adolescents are likely to have health insurance[54,55] and consistent contact with medical providers. In a study from our health system, insured adolescents averaged 1.5 visits to a primary care provider each year.[56] This contrasts with young adults, who despite insurance expansions, still experience high rates of being uninsured and face reduced primary care access.[55,57-60]

The 2017 Guidelines recommend that for otherwise healthy children, BP should be measured annually while youth with obesity or other HTN risk factors should have BP measured at every clinical encounter.[9] Although the cost-effectiveness of BP screening in adolescents has been questioned,[61] there is strong evidence that providers are measuring BP during pediatric and adolescent preventive care visits.[62,63] Early identification of HTN may help children and families adopt lifestyle changes needed to reduce their risk for long-term cardiovascular sequelae. The 2017 Guidelines provide detailed recommendations for the management of elevated BP and HTN in youth. Timing of repeat BP measurements and indications for treatment (lifestyle intervention, antihypertensive medication, or both) are based on the level of BP elevation, whether the elevation is incident or persistent, and whether the adolescent is overweight. For children and adolescents 6 years and older with new onset HTN who are overweight or obese, have a family history of HTN and do not have signs of a secondary cause for HTN, the 2017 Guidelines indicate that an extensive work-up is not needed.[9]

Despite potential benefits of early identification, HTN in children and adolescents is often not recognized.[12,20,37] In an electronic database review of more than 500 youth who met clinical criteria for HTN, only 26% had a HTN or elevated BP diagnosis.[37] Similarly, in a manual chart review of more than 700 pediatric primary care visits in which an elevated BP was recorded (≥90% or ≥120/80 mm Hg), only 13% were clinically recognized, defined as repeating the BP, diagnosing elevated BP or HTN, planning to recheck the BP, or initiating a workup for HTN.[20] A retrospective cohort study of 196 ambulatory clinics within a large practice-based research network found that only 23% of youth who met criteria for HTN were diagnosed.[12] The need for practical and sustainable approaches to implementing the 2017 Guidelines has been identified as a pediatric HTN research gap.[64]

Low rates of recognition and low adherence to pediatric BP guidelines are likely due to barriers in knowledge, attitudes, and behaviors.[21] Providers may not be familiar with clinical criteria for HTN in youth. Competing demands at primary care visits are common and may crowd out time to address BP. In addition, despite recent updates, the classification of HTN is complex and time consuming.[20] The systolic BP (SBP) and DBP cutoffs for the 95th percentile, needed for children 12 and younger, vary by sex, age, and height percentile; without clinical decision support (CDS), patient BP data over time must be interpreted using a series of tables. For example, a table illustrating height-based SBP cutoffs for a 12-year-old girl is shown in Table 1.

Table 1. Height-based systolic blood pressure cut-offs for a 12 year-old girl, from the 2017 Guidelines[9]

BP category	Height percentile						
	5th	10th	25th	50th	75th	90th	95th
Stage 1 HTN (95th%)	118	119	120	122	124	125	126
Stage 2 HT (95th%+12 mmHG)	130	131	132	134	136	137	138

In summary, lack of familiarity with HTN definitions, low clinician buy-in for HTN guidelines, time pressures in providing comprehensive care for children and adolescents,[65,66] complexities of the current BP tables, and the need to review several previous BP measurements to diagnose HTN all contribute to under recognition. CDS, integrated within an existing EHR platform and delivered at the point of care, is ideally suited to address barriers to HTN recognition and management.[67] Automated calculations of BP percentiles for current and prior visits can reduce the time needed to identify an incident or persistently elevated BP. Computer prompts regarding BP classification, recommended evaluations, and timing for follow-up can assist providers unfamiliar with pediatric BP guidelines.

CDS systems have been available for more than five decades, with designs adapted to accommodate changes to clinical practice. Despite this long history, CDS is still an underutilized tool across clinical settings.[68] In a meta-regression of 162 computerized CDS systems, improvements in either patient outcomes or care processes (e.g., provider actions) were seen in just 58% of trials.[69] CDS systems had higher odds of improving patient outcomes if targeting both patients and providers and when the CDS was developed by the respective study authors.[69] A more recent systematic review found that providing CDS automatically, versus on demand, and displaying CDS on a computer screen, versus on paper, both led to moderate improvements in CDS effectiveness.[70] While a unified framework for developing CDS does not yet exist,[68] the GUIDES checklist may prove to be useful for implementing guideline-based CDS such as PedsBP.[71] The GUIDES checklist[71], developed based on opinions from international CDS experts, patients, and other healthcare consumers, encompasses four domains: context related to potential CDS success, CDS content, the CDS system, and implementation of the CDS into practice.[71] The CDS tool that we developed, implemented, and evaluated at HealthPartners (HP) provided patient-centered CDS at the point of care improved the quality of BP measurement and dramatically increased provider recognition of HTN. Development and implementation of the CDS at HP was consistent with best practices and informed by local input from nursing and clinical leadership.[22] The PedsBP CDS was well accepted by providers and is now live in 55 primary care clinics and 17 subspecialty clinics within HP, a large integrated health system.

Compared to urban youth, children living in rural regions have higher rates of obesity[72] and thus are at increased risk for HTN and future cardiovascular disease. Yet, youth in rural regions also experience reduced access to pediatricians and pediatric subspecialists.[29,30,73] Thus, expanding PedsBP CDS for use in a large, primarily rural health system such as Essentia Health (EH) may fill an important gap in care and ultimately lead to improvements in population health. Although the prevalence of HTN in youth is 2-5%[10-12], a review of data from patients 6-17 years with a visit to an EH

primary care clinic and at least one BP measured over an 18-month period found that less than 0.3% had ever been diagnosed with HTN.

Even when an EHR-linked CDS is effective in the setting where it was initially developed, implementation in a new environment, such as a new health system, is prone to challenges.[27] Adoption and effectiveness in the new setting may be impacted by differences in: workflow, EHR configuration, clinic culture, and patient preferences. Implementation strategies can vary in intensity from online webinars or email updates regarding changes to the EHR, to comprehensive in-person training with audit-feedback of use rates. While high-intensity implementation approaches including on-site training may increase adoption, these may also be challenging to implement in rural health systems such as EH, where clinics span a geographic region of over 400 miles. Optimal approaches to implementation of CDS in a new health system, and particularly in a rural health system, have not been well described.[28] Building upon the extensive track record of the HP- and EH-based research teams,[1,2] the proposed research represents a unique opportunity to improve health in an at-risk, rural population.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

All study aspects are considered minimal risk as our intervention promotes care that is consistent with national guidelines and interview and survey information collected is not considered sensitive. CDS recommendations provided as part of the PedsBP CDS intervention are designed to support clinicians' decision-making, not to override clinical judgment.

Risks to provider and rooming staff study subjects are considered minimal and principally involve consideration of the risk of violation of confidentiality of study data. If confidentiality were breached and quality of care were seriously out of range for one or more providers, EH leadership could conceivably use this information to release one or more providers from employment with EH. Therefore, no identifying information on individual provider performance with respect to the clinical domains addressed in this study or any other aspect of care gathered as part of this research project will be made available to EH leaders who make employment, compensation, or disciplinary decisions.

Potential risks to study subjects who are patients include the possibility that the intervention may provide CDS advice to providers on the basis of the 2017 Guidelines, national standards of care for BP in children and adolescents that may be inappropriate for a given individual patient and, if applied without further checking the clinical status of a given patient, could lead to erroneous therapy, adverse events, disability, or death. However, the clinical recommendations are primarily related to proper measurement of height and BP, lifestyle advice, and visit intervals. Therefore, the risk of untoward consequences of such clinical actions is considered minimal. Moreover, this potential risk is routinely present in every clinical encounter within the health care system. We have described below the methods used to minimize this risk.

Additional risks to patients are also minimal and include principally the risk of violation of confidentiality. To protect patient confidentiality, we will create an analytic dataset that includes only encrypted study identifiers. The analytic dataset will be created from various databases that include patient identifiers (names (temporary) and dates). We will use an encryption algorithm to create the encrypted study identifiers. The table that maps encrypted study identifiers to patient identifiers will be stored at EH. We will also adhere to all requirements imposed by the governing Institutional Review Board (IRB) and legal requirements such as HIPAA.

2.3.2 KNOWN POTENTIAL BENEFITS

No claim is made in communications with provider or rooming staff study subjects that any personal benefit will accrue from participating in this project.

Providers will have no defined benefits from participating in this project. However, the CDS is designed to optimize identification and management of BP in children and adolescents and may familiarize some providers with new and potentially useful information that can be used to improve their clinical care. Providers will not receive monetary compensation for time devoted to the study, other than a small payment for completion of the surveys.

Patient study subjects and their parents or legal guardians will have no defined personal benefit from participating in this project and will receive no compensation. No communication between research team members and study subject patients is planned as part of the study protocol. Although some patients may receive earlier identification or management of BP as a result of this intervention, no claim of clinical benefit to an individual patient can or will be made.

2.3.3 PROTECTION AGAINST RISK

The following measures will be taken to protect providers and patients from the risk of breach of confidentiality: A unique study ID code unrelated to the medical record number or other study subject-specific information will be assigned to each patient and provider study subject and used to link data from various sources and needed for analysis. A crosswalk table linking this code number to a provider, patient name or medical record number will be destroyed within 12 months after completion of the linked databases needed to test study hypotheses. The rooming staff and PCP interviews and survey consent procedures will be reviewed in advance, approved, and monitored on an ongoing basis by the IRB.

The following measures will be taken to minimize the risk that a provider will act wrongly on the basis of information provided through CDS developed for this study: Each project-related communication to providers will include a written explanation indicating that the CDS is a suggestion, not a mandate, and that the action should only be taken if judged to be clinically appropriate by the treating provider on the basis of the patient's health, previous health care, current treatment, and other factors.

2.3.4 VULNERABLE SUBJECTS

The study will include children and adolescents 6 to 17 years old at study entry (index visit). Aims of the study are to improve BP care and HTN recognition in children and adolescents, as they are a population at risk for having their HTN not clinically recognized. As such, it is necessary that this study involves children as research subjects. This study is minimal risk as our intervention promotes care that is consistent with national guidelines. It is important to systematically address elevated BP and HTN in this age-group, as children and adolescents have been excluded or underrepresented in previous research studies. To ensure that CDS recommendations for identification and management of elevated BP are appropriate for these patients, we will exclude pregnant or postpartum adolescents. Patients with a known HTN diagnosis or those taking antihypertensive medication will still qualify for CDS-triggered alerts but, because their HTN is not new-onset, they will be excluded from analyses.

The study is specifically designed to include study subjects age 6-17 years old at entry, with up to 12 months of subsequent follow-up. Thus, all patient study subjects are classified as children when they enter the study. There are a number of clear and compelling reasons why those under age 18 years are included in this study:

1. Elevated BP in children and adolescents is associated with elevated BP in adulthood and with subsequent increased risk of untoward clinical events related to elevated BP (strokes, renal failure, myocardial infarction) later in life.
2. Identification and clinical care for elevated BP and HTN in children and adolescents is far from what is currently recommended by the 2017 Guidelines. Thus, research to guide care improvement is justified and necessary. To identify those with elevated BP, providers must interpret measured BP values in the context of age, gender, and height percentile. EHR technology provides a powerful tool ideally suited to translate raw BP data into BP percentile data, and to assess patterns of data over multiple visits to correctly classify those with elevated BP or HTN. The same technology can then be used to provide patient-specific point-of-care clinical decision support based on correct BP classification and the 2017 Guidelines.
3. Because both the definition of elevated BP and BP-related care recommendations are substantively different for children, adolescents and adults, it is important to conduct research specifically with children and adolescents.

Therefore, it is very appropriate to conduct this research project with children and adolescents and their care providers to address distinct problems related to elevated BP and HTN in adolescents.

Dr. Kharbanda, study Co-PI is a Board-certified pediatrician and subspecialty Boarded in Adolescent Medicine. She has over 15 years prior experience conducting research in children and adolescents, including 2 large NIH-funded cluster randomized trials using CDS tools to improve pediatric care.

Dr. Benziger, study Co-PI is a Board-certified cardiologist and medical director of heart and vascular research at a large rural healthcare system. She has a Master of Public Health in epidemiology and is an expert in cardiovascular disease prevention and clinical trials, including site PI of multiple pragmatic randomized clinical trials through Patient-Centered Outcome Research Institute (PCORI) aimed at reducing cardiovascular disease burden.

3 OBJECTIVES AND ENDPOINTS

Overall goals are to evaluate the effectiveness of the PedsBP CDS and to compare low- and high-intensity approaches to CDS implementation. We will adapt the PedsBP CDS for use at Essentia Health and to measure the implementation processes and outcomes.

We may use the GUIDES checklist to assist us in improving use of the CDS, and will frame our implementation based on the following four domains: 1) CDS context, 2) CDS content, 3) CDS system, and 4) CDS implementation.[71]

There are two primary outcomes. One is repeat BP measurement during the same clinic visit, of an initial BP that is ≥95th percentile for children 6-12 years or ≥130/80 mmHg for adolescents 13-17 years. Repeat BPs can be measured by providers or rooming staff but will only contribute to this outcome if recorded in the vitals section of the EHR. The other primary outcome is clinical recognition of HTN within 6 months of meeting criteria for HTN. Post-implementation comparisons of high- plus low-intensity implementation versus usual care and high- versus low-intensity implementation interventions will be conducted for the primary endpoints of BP remeasurement at the index visit (for patients with an elevated first BP), and BP recognition within 6 months of the index visit (for patients newly meeting HTN criteria).

In secondary analyses we will evaluate the impact of the adapted PedsBP CDS on management of HTN including diet and exercise counseling, provision of antihypertensive medications, subspecialty referrals, and diagnostic testing. In

addition, among youth newly meeting criteria for HTN, we will explore differences in BP control at 12 months. This research builds on prior research in pediatric and adolescent HTN[10,16,23,31,32], cardiovascular disease,[33,34] and CDS development and implementation.[22,24,35] Our multidisciplinary team seeks to improve the quality of BP measurement, increase HTN recognition, and promote guideline adherent management of HTN in rural youth — all necessary first steps towards improving cardiovascular health in this population.

4 STUDY DESIGN

4.1 APPROACH TO ADAPTATION AND IMPLEMENTATION

4.1.1 PHASE 1 – ORGANIZATIONAL ENGAGEMENT AND PILOT TESTING

Organizational Engagement

We will engage EH clinic leadership and managers, informatics personnel, providers, and rooming staff, through meetings to review standard clinical workflow (e.g., timing of: BP measurement, height measurement, entry of height and BP data into the EHR, and clinician review of EHR data) along with variance in these processes across clinical sites. As in our prior studies, we will work with leadership to identify potential barriers and facilitators that would influence adoption of the CDS.[96] All PedsBP algorithms and interfaces will be extensively reviewed by EH stakeholders prior to implementation. EH has 18 volunteer patient advisory councils that engage patients and families as advisors, mentors, and educators. The main goal of this program is to improve the patient and family experience and quality of healthcare. With guidance from our consultant, Dr. Joseph Konstan, from the University of Minnesota, the EH research team will recruit representative members to review and critique PedsBP CDS interfaces and associated educational material.

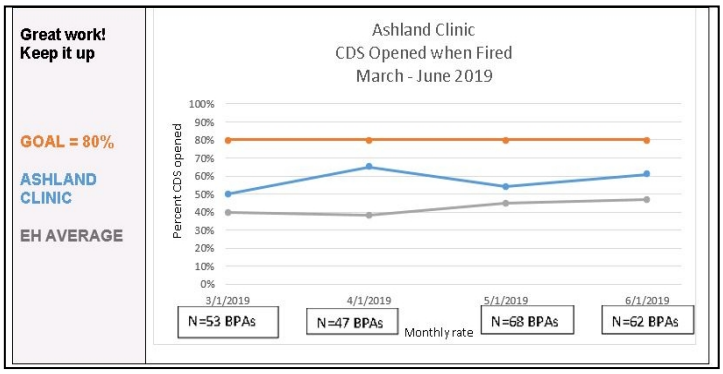
Pilot Testing

With approval from clinical leaders to proceed, we will then recruit one rural and one urban EH clinic not in the full intervention study and pilot the PedsBP CDS for up to six months. The purpose of the pilot is to verify that 1) we are capturing all data elements needed for intervention analysis, 2) test all components of the CDS algorithms, to make sure they are working as designed/intended, 3) refine algorithms ahead of full intervention. Additional quality assurance will be done on a random sample of patients identified as eligible for receiving the CDS via chart reviews to ensure data accuracy (see Section 9.1.4 for more on quality assurance and testing). During the pilot we will also conduct in-depth interviews with providers and rooming staff at pilot clinics, asking probing questions (e.g., 'How does the CDS fit in your workflow?', 'Was the CDS useful'?, 'Was the CDS disruptive?', 'Did the CDS help you in making a decision about your patient's blood pressure management?', 'How can the study team facilitate use of the CDS'?) about the PedsBP CDS, aiming to identify facilitators and barriers to use (separate interview-specific protocol will be submitted). Up to six months is allotted for the pilot, allowing for an iterative process of piloting, feedback from providers and rooming staff, modifications to the CDS display, wording of recommendations or criteria for triggering BPAs, as needed, with subsequent piloting of the modified tool. In addition, the long pilot period may be needed to ensure that providers and rooming staff have sufficient exposure to the CDS, including for patients newly meeting criteria for HTN (expected background rate 2-3%). Upon reaching a stable CDS platform with general acceptance from providers and clinic staff, the project will move to Phase 2, the full intervention.

4.1.2 PHASE 2 – FULL INTERVENTION

We will randomize clinics to one of three arms and will utilize the 'Educate' intervention strategy, varying by intensity, as described by Powell et al.[97] The low-intensity intervention clinics may receive education and training following standard practice for delivering any updates to primary care at EH. Within two weeks of our go-live date, providers and rooming staff would receive an email with links to a short instructional video demonstrating provider and rooming staff roles in the PedsBP CDS. The clinics randomized to the high-intensity implementation may be offered the same e-learning, with reminders to view the online training video using EH's internal learning assignments. In addition, at high-intensity clinics study personnel may conduct in-person or video conference training for available providers and rooming staff. These in-person trainings may occur within eight weeks of our go-live. Following implementation, high-intensity clinic staff may receive monthly email reports showing PedsBP use rates. An example, adapted from an ongoing CDS project at EH, is shown in Figure 1.

Figure 1. Example of Peds & TeenBP Use Report



In addition, the project manager may meet either in-person or remotely with each high-intensity clinic's nurse manager monthly throughout the intervention period to assess continued use of PedsBP and to gather feedback ensuring real-time observation of implementation fidelity. Support from EH leaders and clinic providers, along with monitoring and feedback, will help maximize adoption of PedsBP, as demonstrated by CDS use at 75%-80% of targeted visits in previous projects.

To further encourage use of the tool, high-intensity clinics may be offered a best practice 'lunch and learn' for CDS usage at goal. If a clinic achieves four non-consecutive months at or above 75% usage rate, the PedsBP team will provide a catered project-related meeting. The team will provide a meeting agenda for the clinic manager and/or nurse supervisor with the expectation that notes from the meeting will be returned to the team. This 'lunch and learn' may also be offered at 10 non-consecutive months at or above 75% CDS usage.

4.1.3 PHASE 3 – ANALYSES

This period encompasses analyses, reporting of key study results, and implementation of the intervention in the non-intervention clinics, if requested by EH. Throughout the study, there will be ongoing analysis of data as they become available, and preliminary results will be presented at meetings and/or reported in peer-reviewed articles.

5 STUDY POPULATION

In this study, we aim to evaluate the PedsBP CDS in up to 45 primary care clinics with an estimated total of 216 primary care providers and 360 rooming staff. The majority of sites are staffed by family practice physicians (n=31). Pediatricians (n=2), both family practice and pediatricians (n=4) or advanced practice providers alone (n=8) cover the remaining sites.

Based on prep data, we estimate that over the 18-month study period there will be 44,061 unique patients 6-17 years with BP, height and weight recorded, with an average of 2.02 visits per patient over the study period. Similar to demographics of the region, the population is 90% white, non-Hispanic. Fifteen percent of youth receiving care at these sites are obese, with BMI ≥95th percentile. Elevated BP is common (10-20% of patients with at least 1 BP meeting

criteria for elevated BP), yet diagnoses for hypertension were only found in 120 (<0.3%).

5.1 INCLUSION CRITERIA

Patients will be eligible for the PedsBP CDS tool if:

a) 6-17 years of age
b) BP measured and entered in the vital sign section during an ambulatory primary care visit in a randomized primary care clinic
c) not pregnant or postpartum

Patients must meet these eligibility criteria to be included into study analyses:

a) have at least one index visit to a randomized primary care clinic in the intervention period
b) meet eligibility for PedsBP CDS at index visit
c) no previous HTN diagnosis prior to index visit
d) not taking antihypertensive medication prior to index visit
e) not opted out of use of their data for research via general consent prior to performing analyses

Primary care providers must meet these eligibility criteria to participate in this study:

a) practice at a randomized primary care clinic
b) be a pediatric or family medicine care provider (pediatrician, family physician, nurse practitioner or physician assistant), and
c) provide ongoing clinical care for children and adolescents

Provider and rooming staff inclusion criteria for interviews and surveys are provided in separate protocols.

5.2 EXCLUSION CRITERIA

Patients will be excluded from analyses if the following criteria are met:

a) outside of the inclusion age range (<6 years and ≥18 years) at index visit
b) pregnant or postpartum adolescents during study period
c) known HTN diagnosis or taking antihypertensive medication at index visit
d) opted out of use of their data for research via general consent prior to performing analyses

Provider and rooming staff exclusion criteria for interviews and surveys are provided in separate protocols.

6 STUDY INTERVENTION(S)

6.1 STUDY INTERVENTION(S)

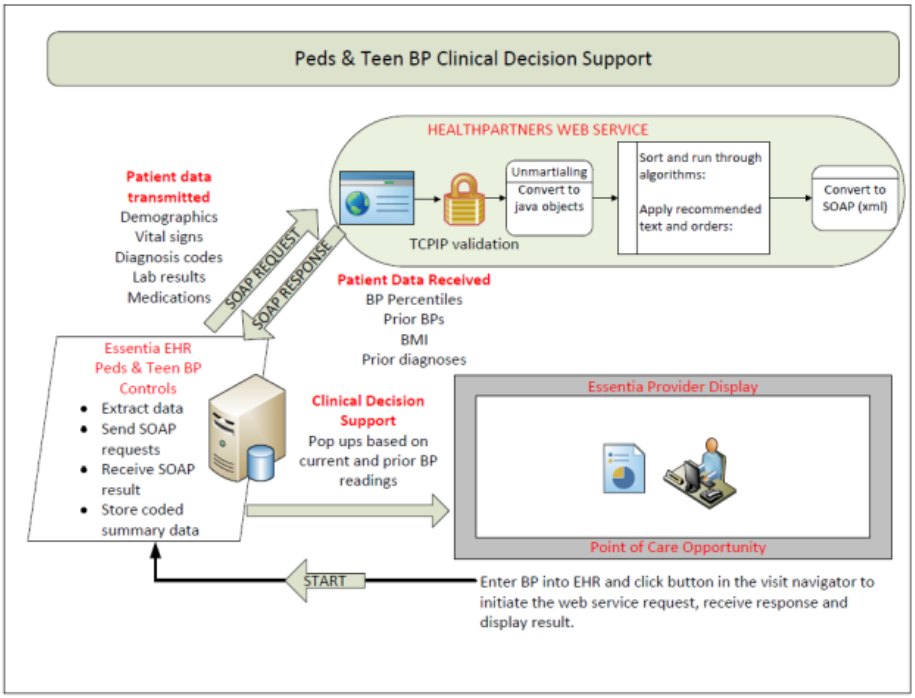
6.1.1 DESCRIPTION OF CDS INTERVENTION

The PedsBP CDS will be integrated within the EHR (EPICare, Verona, WI) with data transfer to and from a web service, based at HP, for data processing. PedsBP CDS will be activated when a patient 6-17 years has a BP measured and entered in the vital sign section of the EHR during an ambulatory primary care visit in a randomized study clinic. Eligible patients will be allocated to the study arm assigned to their clinic at their index visit. Figure 2 illustrates how data would flow from the EHR to and from the HP-based web-service for the proposed study.

The PedsBP CDS tool includes seven key features:

(i) a best practice advisory (BPA) regarding the need for height data to classify the BP by percentile
(ii) a BPA to repeat any BP that is ≥95th percentile or ≥130/80 mm Hg
(iii) classification of current and prior BPs in the prior two years and identification of BPs in stage 1 HTN and stage 2 HTN range
(iv) review of previous HTN diagnoses and BPs in order to classify an elevated BP at the current or index visit as a first or second elevated BP, or as meeting criteria for HTN
(v) review of medications and diagnoses that may affect BP
(vi) tailored CDS based on HTN category and previous diagnoses
(vii) graphical representation of current and prior BP data by age and BP percentile.

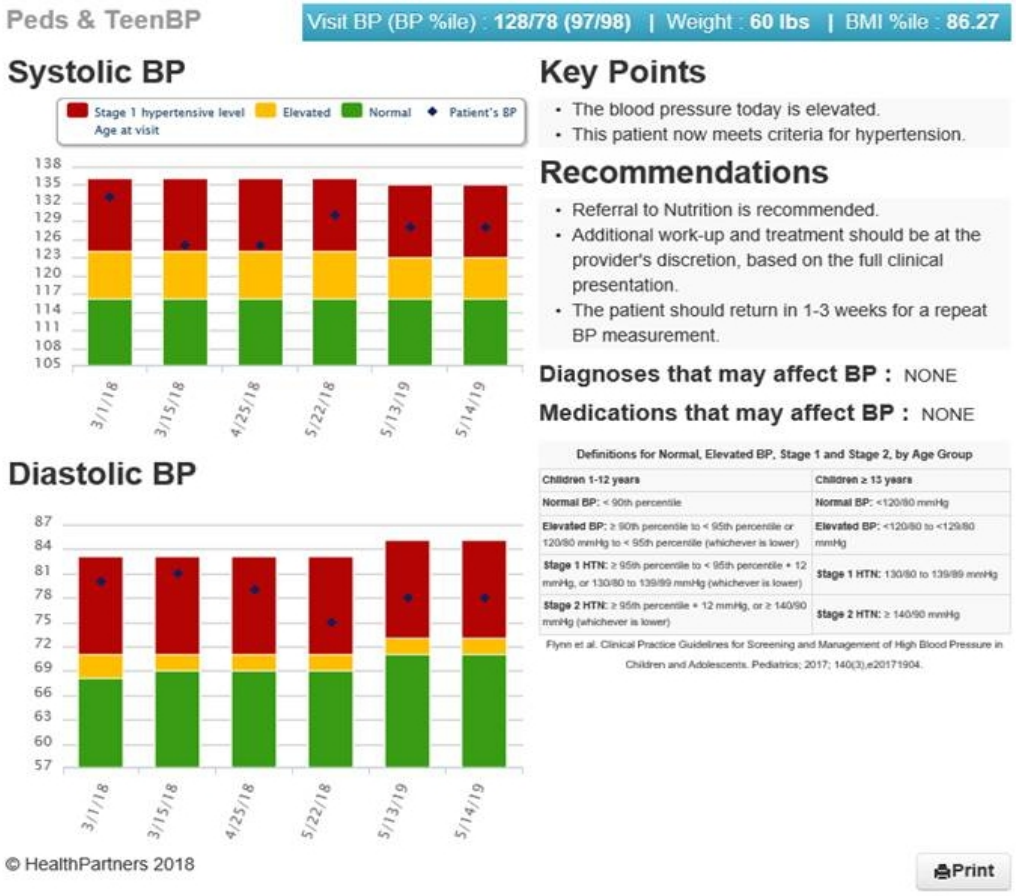
Figure 2. Peds & TeenBP CDS Data Capture



Each of these features is described below in Figure 3.

The first component of the CDS is a BPA to ensure a current height measurement for children 12 and under (needed to compute BP percentiles): (a) If a height is entered at the visit, it will be used; (b) If no height is entered when entering a BP, the closest antecedent height recorded within 1 year is used to calculate a BP percentile, assuming a constant height percentile. If there is no height available for the current visit or the prior 12 months, a BPA displays requesting a height be measured and recorded in the EHR. As height measurement is standard in pediatric care, this BPA is currently firing in less than 1% of visits.

Figure 3. Example of Peds & TeenBP CDS for 6-year old meeting criteria for Stage 1 HTN



The second component of the CDS, a BPA to repeat an elevated BP, is triggered for BPs ≥95th percentile in children 6-12 years or ≥130/80 mmHg in youth 13-17 years when the BP is entered into the vital signs section of the EHR, and the vital signs box is closed.

In the third component, the CDS will use the lowest SBP for that visit to assign BP percentiles and classify BPs as normotensive, elevated BP, stage 1 HTN, or stage 2 HTN. If the initial elevated BP is not repeated, the BP percentile will be calculated for the available measurements. BP percentiles are calculated as in Appendix B of the Fourth Report[36] and include the new reference population, as described in the 2017 Guidelines.[9]

In the fourth component of the CDS, for patients with BP ≥95th percentile (6-12 years of age) or ≥130/80 mmHg (13-17 years of age), the CDS reviews data pulled from the EHR including prior HTN diagnoses, prior BPs and heights. The index and previous BPs and diagnosis data are used to categorize elevated BPs as incident or persistent, and to determine whether a patient meets clinical criteria for new onset stage 1 or stage 2 HTN, or pre-existing HTN.

In the fifth component of the CDS, current medications (e.g., oral steroids or stimulants that increase BP or diuretics that lower BP) and prior diagnoses that may affect BP are displayed. In addition, current body mass index (BMI) and BMI percentile are calculated. For patients meeting criteria for obesity, BMI ≥95th percentile with new onset HTN, obesity is noted in the CDS as a potential cause for the HTN.

In the sixth component of the CDS, providers receive tailored CDS for BPs ≥95th percentile or ≥130/80 mmHg. The CDS recommendations are specific, based on the magnitude of BP elevation (stage 1 or stage 2 HTN) and whether the BP is

incident or persistent. If the patient has a prior diagnosis of HTN, the CDS provides tailored feedback regarding whether the BP is at goal (<95th percentile) or elevated and possibly requires initiation or a change in medication.

In the seventh component of the CDS, current and previous SBPs and DBPs, within the last 2 years are graphed and displayed, with elevated BP, stage 1, and stage 2 HTN BP cutoffs specified. This feature allows providers to visualize patient-level variability and trends in BP over time. In addition, the CDS can be printed for families, to assist with shared decision making. An example, including the display of BPs over time, is shown in Figure 3.

6.2 RANDOMIZATION STRATEGY

Covariate-based constrained randomization[98] may be used to enhance study arm balance on key factors during randomization of the clinics in this cluster-randomized trial. This method permits the use of multiple balance factors and can yield improved study arm balance and increased statistical power beyond simple randomization when balance factors are included in both the design and analysis phase[99] of the study. Clinic-level attributes of clinics and patient mix to be used as balance factors will be obtained via EHR data and ascertained for care in clinics in the 18 months prior to randomization. Proposed clinic-level balance factors include baseline levels of BP re-measurement and HTN recognition, number of visits with patients age 6-17 (ranging from 145 to 6556 patients per clinic over 18 months in preparatory data), location (metropolitan/micropolitan (20 clinics) versus small town/rural (25 clinics)), and proportion of public pay patients (ranging from 13% to 73%). Randomization will be carried out with the CCR macro for use within SAS[100], and conducted one month prior to implementation of the low- and high-intensity strategies in clinics.

7 TRAINING REQUIREMENTS

7.1 OVERALL TRAINING APPROACH

Training for clinics in low- and high-intensity arms will be developed to incorporate general training, study-specific training, and mechanisms for competency assessment. The study team is responsible for the development of a comprehensive Training Plan, instructional material, and delivery of the training (e.g., via self-study, webinar, or teleconference). Within primary care clinics randomized to receive the PedsBP CDS, rooming teams will be trained on how to recognize the PedsBP alerts and may receive basic education on BP measurement and HTN; PCPs will be trained on how to use the PedsBP CDS. Training instructions will include how to let the study team know of any issues or questions. Traditionally, we have completed such trainings at in-person lunch meetings with clinic personnel, but will also consider other training modalities, such as web-based trainings or teleconferences, depending on the standard training practices and clinic leadership preference.

8 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL HYPOTHESES

Specific Aim 1: Among youth 6-17 years with an elevated BP measurement (≥95th percentile or ≥130/80 mmHg), to evaluate the effectiveness of the adapted PedsBP for repeat BP measurement:

Hypothesis 1: Youth with elevated BP measured at a PedsBP intervention clinic will be more likely to have a repeat BP

measurement during their visit as compared to those attending usual care clinics.

Hypothesis 2: Youth with elevated BP measured at a high-intensity PedsBP clinic will be more likely to have a repeat BP measurement during their visit, as compared to those attending low-intensity PedsBP clinics.

Specific Aim 2. Among youth 6-17 years meeting criteria for HTN, to evaluate the effectiveness of the adapted PedsBP for improving HTN recognition:

Hypothesis 3: Youth meeting criteria for HTN at a PedsBP intervention clinic will be more likely to be clinically recognized within 6 months of their index visit, as compared to those attending usual care clinics.

Hypothesis 4: Youth meeting criteria for HTN at a high-intensity PedsBP clinic will be more likely to be clinically recognized within 6 months of their index visit, as compared to those attending low-intensity PedsBP clinics.

Table 2. Study Contrasts and Outcomes by Hypothesis

Hypothesis	Contrast	Denominator	Outcome(s)	Data source(s)
H1	CDS (low- or high-intensity) *versus* Usual care	First BP at visit ≥95th percentile (ages 6-12) or ≥130/80 mmHg (ages 13-17)	Repeat BP measured and recorded at same visit	Automated BP data from EHR or CDS
H2	CDS low-intensity *versus* CDS high-intensity			
H3	CDS (low- or high-intensity) *versus* Usual care	BP at visit and at least 2 of 4 prior BPs, within last 2 years, ≥95th (ages 6-12) or ≥130/80 mmHG (ages 13-17)	HTN recognition within 6 months of meeting criteria for HTN	Automated data from EHR or CDS
H4	CDS low-intensity *versus* CDS high-intensity			
Secondary / Exploratory	CDS (low or high intensity) *versus* Usual care	BP at visit and at least 2 of 4 prior BPs, within last 2 years, ≥95th (ages 6-12) or ≥130/80 mmHG (ages 13-17)	Management within 6 months of meeting criteria for HTN including: Lifestyle counseling, Referrals, Medications for HTN, Diagnostic imaging / BP at 12 months Provider satisfaction	Automated data from EHR or CDS, limited chart review and provider survey

8.2 SAMPLE SIZE DETERMINATION

Aim 1. Preliminary data from EH indicate there were 44,061 unique patients age 6-17 with visits to the 45 largest EH primary care clinics in an 18-month period. This data also indicates that 16% (n=7,258) of patients age 6-17 years had an elevated BP at initial measurement and BP re-measurement occurred at 30% (n=2210) of encounters with an elevated BP. The initial PedsBP trial had a clinic-level ICC for BP re-measurement of 0.03 and BP re-measurement of 28% in UC and 47% in the PedsBP arm.[23] With an expected 7,258 patients (161 per clinic), this study has 99% power for the H1 comparison of low- plus high-intensity clinics (30 clinics) with 15 UC clinics (alpha=.05, two-sided test, ICC=0.03) to detect a raw BP re-measurement difference of 15% between the usual care arm (30%) vs. low- plus high-intensity arms (45%). The minimum detectable difference with 80% power is 8% (30% UC vs. 38% low- plus high-intensity arms). With an expected 4,840 patients (161 per clinic), this study has 80% power for the H2 comparison of low-intensity (15 clinics, 2420 patients) vs. high-intensity clinics (15 clinics, 2420 patients), with alpha=.05, two-sided tests, ICC=0.03, to

detect a minimum detectable difference in BP re-measurement of 10% between the low-intensity arm (40%) vs. the high-intensity arm (50%).

Aim 2. Based on the prior Peds & TeenBP trial[24], along with observational studies of pediatric HTN[10-12] we anticipate 2% of patients age 6-12 and 3% of patients age 13-17 will newly meet HTN criteria at a visit over 18 months, yielding a sample size of 1060 patients (24/clinic). The PedsBP study found that 21% of patients newly meeting HTN criteria were recognized over 6 months in UC and 55% in the PedsBP arm[24], and the clinic-level ICC for HTN recognition was 0.035. With 1060 patients (24/clinic) and 45 clinics, this study has 99% power (alpha=.05, two-sided test, ICC=0.035) for H3 to detect a difference in HTN recognition of 17% between UC (20%) and the low- plus high- intensity arms (37%), and a minimum detectable difference of 11% (20% UC vs. 31% low- plus high-intensity arms) at 80% power. For H4 the minimum detectable difference at 80% power for HTN recognition among 706 patients (24/clinic) is 14% between low-intensity (30%) and high-intensity (44%) arms. Power computations account for the design effect due to clinic randomization and unequal counts of clinics in some comparisons and were conducted with PASS 2019.

8.3 POPULATIONS FOR ANALYSES

We will continue to engage with EH leadership to ensure the active participation of EH clinics. EH leadership support for this project, as evidenced in the letters of support, ensures the participation of primary care clinics.

Patients 6 to 17 years of age with a BP recorded at a participating EH primary care clinic will be eligible and automatically enrolled on the basis of data recorded in the EHR and captured by the PedsBP CDS. Given that one of the primary purposes of the study is to test the effectiveness of the different intervention approaches, including a high-intensity intervention with additional outreach and engagement of clinicians and rooming staff, we do not plan to conduct additional recruitment or retention activities.

Aim 1 outcomes will be assessed in the context of care provided at the index visit with an isolated hypertensive BP recorded. Aim 2 outcomes will be assessed over a period of 6 months following when a patient meets criteria for HTN. Clinical recognition of HTN, dietitian or other lifestyle referral and lifestyle counseling will be assessed based on care received. There will be no additional efforts to recall patients for additional study visits. For subjects with no follow-up visits, Aim 2 outcomes will be assessed based on clinical actions at the index visit.

Providers and rooming staff will be invited to participate in surveys and in-depth interviews through email or in-person recruitment by EH study staff. Surveys and interviews will be conducted at the time of recruitment as well as through a follow-up survey at the end of the intervention period. We will work with clinic administrative staff as necessary to help coordinate interviews and surveys with clinicians and rooming staff in a way that is not disruptive to regular clinic operations.

Data sources

Data required for PedsBP CDS-enhanced care will be sent to HPI for PedsBP operations. CDS data is retained in the transactional data store with minimal access until needed for analysis. With respect to the transactional data store, the following measures will be taken to protect PCPs and patients from the risk of breach of confidentiality: A unique study ID code unrelated to the medical record number or other study subject-specific information will be assigned to each patient at the index visit (first visit in the intervention period). The study ID is used to link data from patient encounters over time and various data sources that are needed for analysis. All index and subsequent encounter data for eligible patients, including vitals, medications and diagnoses, are securely stored behind a firewall within a limited de-identified dataset.

A crosswalk table linking this code number to a medical record number or patient name will be created by EH programmers in order to 1) check against opt out lists, and 2) link to study outcomes. EIRH Informatics Analysts assigned to this research project will exclude patients who have opted out via general consent; data for these patients will not be stored in analytic data files. The data for patients who have opted out of external research will be deleted from analyses files. The crosswalk will be destroyed within 12 months after completion of the linked databases needed to test study hypotheses. This project will be governed by a Business Associates Agreement, DUA, and appropriate services agreements.

8.4 STATISTICAL ANALYSES

Aim 1. Preliminary data from EH indicate there were 44,061 unique patients age 6-17 with visits to the 45 largest EH primary care clinics in an 18-month period. This data also indicates that 16% (n=7,258) of patients age 6-17 years had an elevated BP at initial measurement and BP re-measurement occurred at 30% (n=2210) of encounters with an elevated BP. The initial Peds & TeenBP trial at HealthPartners had a clinic-level ICC for BP re-measurement of 0.03 and BP re-measurement of 28% in UC and 47% in the Peds & TeenBP arm.[23] With an expected 7,258 patients (161 per clinic), this study has 99% power for the H1 comparison of low- plus high-intensity clinics (30 clinics) with 15 UC clinics (alpha=.05, two-sided test, ICC=0.03) to detect a raw BP re-measurement difference of 15% between the usual care arm (30%) vs. low- plus high-intensity arms (45%). The minimum detectable difference with 80% power is 8% (30% UC vs. 38% low- plus high-intensity arms). With an expected 4,840 patients (161 per clinic), this study has 80% power for the H2 comparison of low-intensity (15 clinics, 2420 patients) vs. high-intensity clinics (15 clinics, 2420 patients), with alpha=.05, two-sided tests, ICC=0.03, to detect a minimum detectable difference in BP re-measurement of 10% between the low-intensity arm (40%) vs. the high-intensity arm (50%).

Aim 2. Based on the prior Peds & TeenBP trial[24], along with observational studies of pediatric HTN[10-12] we anticipate 2% of patients age 6-12 and 3% of patients age 13-17 will newly meet HTN criteria at a visit over 18 months, yielding a sample size of 1060 patients (24/clinic). The Peds & TeenBP study found that 21% of patients newly meeting HTN criteria were recognized over 6 months in UC and 55% in the Peds & TeenBP arm[24], and the clinic-level ICC for HTN recognition was 0.035. With 1060 patients (24/clinic) and 45 clinics, this study has 99% power (alpha=.05, two-sided test, ICC=0.035) for H3 to detect a difference in HTN recognition of 17% between UC (20%) and the low- plus high-intensity arms (37%), and a minimum detectable difference of 11% (20% UC vs. 31% low- plus high-intensity arms) at 80% power. For H4 the minimum detectable difference at 80% power for HTN recognition among 706 patients (24/clinic) is 14% between low-intensity (30%) and high-intensity (44%) arms. Power computations account for the design effect due to clinic randomization and unequal counts of clinics in some comparisons and were conducted with PASS 2019.

Hypotheses 1 and 2 for **Aim 1** posit that patients with an elevated BP seen at clinics with low- or high-intensity PedsBP CDS will be more likely to have their BP re-measured as compared to patients seen at usual care clinics, and that repeat measurement will be more likely for patients seen at high-intensity rather than low-intensity clinics. Because clinics are randomized and the outcome varies at the patient level, generalized linear mixed-model regression with a logit link and binomial error distribution will be used to test the effect of the interventions using the model specified below.

Aim 1, H1: $BP\_Remeasure_{ji} = \gamma_{00} + \gamma_{10}TeenBP_j + \gamma_{20}StratFactors_j + \gamma_{01}PatientCovars_i + [u_{j0} + e_{ji}]$

Aim 1, H2: $BP\_Remeasure_{ji} = \gamma_{00} + \gamma_{10}HighVsLow_j + \gamma_{20}StratFactors_j + \gamma_{01}PatientCovars_i + [u_{j0} + e_{ji}]$

The dependent variable for Aim 1 (BP_Remeasure) is a binary indicator of post-implementation re-measurement of BP at the index visit at which the elevated BP occurred. For H1 this endpoint will be predicted by a fixed effect study arm term ($TeenBP_j$) contrasting low- plus high-intensity PedsBP clinics with usual care clinics, stratification factors used in the clinic randomization ($StratFactors_j$), and patient-level covariates of age, sex, and SBP percentile of the elevated BP. A random intercept for clinics is included (u_{j0}) to account for the clinic-level randomization. The analysis for H2 will contrast high- and low-intensity clinics ($HighVsLow_j$)) and exclude usual care clinics from the analysis, but otherwise be similar to H1. Statistically significant study arm contrasts (alpha=.05) and parameters in the expected direction will support the H1 and H2 predictions stated for Aim 1.

Hypotheses 3 and 4 for **Aim 2** posit that patients who newly meet HTN criteria at clinics with low- or high-intensity PedsBP CDS will be more likely to have their HTN recognized within 6 months as compared to patients seen at usual care clinics, and that recognition of HTN will be more likely for patients seen at high-intensity rather than low-intensity clinics. Generalized linear mixed-model regression with a logit link and binomial error distribution may be used to test the effect of the interventions following the same analytic strategy and equations for H1 and H3 above, with the substitution of HTN recognition as an endpoint in place of BP re-measurement, and the use of patient-level covariates of the lowest SBP percentile at the index visit, and BMI percentile at the index visit. Study arm contrasts will test differences in BP recognition for CDS (low-intensity or high-intensity) *vs*. Usual care and high-intensity *vs.* low-intensity. Statistically significant study arm contrasts (alpha=.05) and parameters in the expected direction will support the H3 and H4 predictions stated for Aim 2.

8.4.1 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Management of HTN within 6 months of meeting criteria will be described, including lifestyle counseling, dietitian referrals, subspecialty referrals, initiation of antihypertensive medications, and diagnostic imaging as individual endpoints in separate analyses and following the analytic approach described above for H3. Heterogeneity of the effects of the two implementation strategies will be examined in pre-specified subgroups defined by age (6-12, 13-17), BMI (>30 vs. <30), sex, and race/ethnicity, as feasible. Models described earlier will incorporate interaction terms of patient factors and study arm fixed effects and utilize study arm contrasts to estimate parameter estimates and standard errors for differences in implementation strategies within these subgroups of patients. We anticipate at least 60% response rate among 214 providers in completing the provider survey. We predict that one or more follow-up BPs within 12 months of meeting criteria for HTN will be available for 70% of patients meeting criteria for HTN at intervention clinics and 50% of patients meeting criteria for HTN at usual care clinics.

9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1.1 INFORMED CONSENT PROCESS

We are requesting a waiver of informed consent of providers and rooming staff, and a waiver of parental permission and child assent of patients, to implement and operate the PedsBP CDS in primary care clinics for the following reasons: (a) All treatment options included in the CDS algorithms are based on current national guidelines, and no other care

recommendations are provided. Thus, the care recommendations provided conform to current standards of care and ought not to represent any risk to patients beyond the routine risk that all patients assume whenever they have contact with the medical care system. (b) At intervention clinic training sessions and on CDS displays in the EHR, we emphasize that the material provided is meant only as a suggestion, not as a mandate, and that it is inappropriate for a provider to follow suggested treatment options without further checking the clinical status of a given patient. (c) It would be impractical to consent or assent patients (due to large numbers) and impossible to answer the primary research questions (due to selection effects related to consent) if informed consent of patients were required.

Because use of PedsBP CDS tool itself is considered usual care and all necessary data to determine eligibility, implement and operate the PedsBP CDS intervention, test the study hypotheses and assess the impact of the intervention are derived from electronic health records (EHRs), waivers of HIPAA authorization, informed consent, parental permission and child assent are being requested to identify and enroll patients who are to be included in the study.

All rooming staff and PCPs will be consented to participate in any interviews or surveys. *DETAILS OF INTERVIEWS AND SURVEYS ARE PROVIDED IN SEPARATE PROTOCOLS.*

9.1.1.1 SURVEY AND INTERVIEW CONSENT PROCEDURES AND DOCUMENTATION

DETAILS OF INTERVIEWS AND SURVEYS ARE PROVIDED IN SEPARATE PROTOCOLS.

The informed consent process is a means of providing study information to each prospective participant and allows for an informed decision about participation in the study. The informed consent forms will include all the required elements of informed consent. Prior to informed consent, research staff will provide a detailed description of the study and interview or survey to the potential participant and provide a copy of the consent to read. If the participant is interested in participating in the interview or survey, he or she will have the opportunity to ask any questions related to participation.

The informed consent forms will be updated or revised whenever important new safety information is available or whenever the protocol is amended in a way that may affect participants' participation in the study. Participants will be informed that their participation is voluntary and they may withdraw from the study at any time, for any reason, without penalty. Individuals who refuse to participate in interviews or surveys or who withdraw will be treated without prejudice.

9.1.2 KEY ROLES AND STUDY GOVERNANCE

For the proposed study, the EH Institutional Review Board (IRB) will serve as the single IRB (sIRB) of record. Prior to implementing the proposed study, EH and HP will sign an authorization agreement specifying roles and responsibilities. If any new organizations are added after the AHRQ award, they too will recognize EH as the sIRB of record for the study and complete an authorization agreement. The EH PI will directly communicate with the EH IRB. EH will maintain all authorization agreements and the IRB communication plan between the participating sites.

Principal Investigator	Principal Investigator	Medical Monitor or Independent Safety Monitor
Catherine Benziger, MD Cardiologist	Elyse Kharbanda, MD Senior Investigator, Pediatrician	Carolyn Bramante, MD Internist, Pediatrician
Essentia Health	HealthPartners	University of Minnesota
218-786-3443	952-967-5038	TBD
Catherine.Benziger@essentiahealth.org	Elyse.O.Kharbanda@Healthpartners.com	bramante@umn.edu

9.1.3 SAFETY OVERSIGHT

The PIs, Drs. Kharbanda and Benziger will be responsible for the safety of the trial and adherence with the study protocol. In addition, we have invited a single medical monitor, independent of the study, Dr. Carolyn Bramante, to lead the Data Safety Monitoring Plan. As in prior work by our group, we will select an independent medical monitor with relevant clinical and research expertise. The intervention provides point-of-care clinical decision support (CDS) to primary care providers designed to identify children and adolescents with elevated BP and HTN and suggests care options that may be appropriate in specific clinical scenarios. Suggestions provided to PCPs are based on national recommendations and will be further vetted by clinical leaders at Essentia Health (EH) prior to implementation. Alerts are designed to support clinicians' decision making, not to override clinical judgment.

The study team will convene within 3 months of the beginning of the intervention at a face-to-face or phone meeting with the independent safety monitor and will meet up to twice annually through the study. The independent safety monitor will provide guidance on the study evaluation and intervention protocols, including quality assurance and safety issues related to the intervention protocols, implementation strategies, and data-handling activities. The independent safety monitor will also provide periodic input and feedback on the progress of study accrual of patients, eligibility determination issues, data completion rates, and adverse events. Consistent with NIH, AHRQ, EH and HealthPartners (HP) policy, the medical monitor is not be affiliated with HP or with EH.

As a minimal risk, pragmatic trial, we do not propose interim analyses or stopping rules. A special focus of interest will be the safety of patients exposed to the study intervention. We will collect data from the electronic health record (EHR) or the CDS to identify potential rare adverse events related to untreated or undertreated HTN, such as malignant HTN or stroke. In addition, using automated methods we will monitor for hospitalizations within 6 months following exposure to the CDS, with additional clinical review regarding any potential for the CDS to have impacted subsequent events. The PIs will be responsible for responding to unsolicited complaints, for reviewing potential serious adverse events, and for additional communications with the IRB and with AHRQ.

9.1.4 CDS QUALITY ASSURANCE AND TESTING

Additional quality assurance (QA) and testing will be conducted to ensure appropriate functioning of the algorithms, which determine clinical recommendations made by the CDS to the provider and patient. Study personnel at EH will be responsible for manual chart review of select patients' electronic medical records. No information will be will collected, used, or disclosed for study analyses.

A full waiver of HIPAA Authorization is requested to access medical record for QA and testing purposes.

9.1.5 DATA HANDLING AND RECORD KEEPING

9.1.5.1 DATA COLLECTION AND MANAGEMENT

Data from the PedsBP CDS will be stored throughout the study, to be linked through a unique study ID with the minimum EHR and administrative data to evaluate study outcomes. Data transfer is secured using certificate-based authentication and IP whitelisting. In addition, data access is secured using FHIR based OAuth protocols.

In compliance with HIPAA regulations[140], no personally identifiable health information (PHI) will be shared outside of the affiliated covered entities (ACE).

The study team has extensive experience in health services research and clinical research with human subjects, with procedures to safeguard privacy and personal information. All study records are protected by:

- Locked storing all paper records in a secure location
- Use of untraceable study ID numbers instead of names wherever possible
- Password protection as well as firewalls
- Strong user login authentication on all electronic devices
- Physical security for all electronic devices containing personal information

We will establish common study variable definitions drawn from national standards and from definitions used in HP's previous studies.[101] We will construct variable definitions and data-extraction procedures for demographics, enrollment characteristics, vital signs, pharmacy, and outpatient encounters and diagnoses. We will develop conceptual and operational definitions and technical specifications for data elements without established definitions. Data from all sources will be restructured into a common format and data elements combined into uniform files. All person-level information will be linked by a unique identifier so data can be compiled to the person level. Data integrity will be assessed to ensure that observations are valid, reliable, and consistent. Each variable will be tested for completeness and out-of-range values. The accuracy of HTN identification,[102] selected laboratory results, BP data, and pharmacy data[103] has been established in previous work in adult cohorts and found to be excellent. Definitions will be adapted from HP's prior Peds & TeenBP clinical trial.[22-24]

9.1.5.2 STUDY RECORDS RETENTION

Data will be retained in secure storage following the completion of the study in accordance with Minnesota and federal law. We guard against the potential for breach of subject confidentiality through a multi-layered system of data protection policies, processes, staff training, software safeguards and physical security measures for both paper and electronic data involved in research.

The following measures will be taken to protect subjects from the risk of breach of confidentiality:

- All data collected in the study will be identified by using a previously assigned arbitrary and unique subject identification number to each participant.
- A file containing a link between the study ID and individually identifying information will be maintained by a EH programmer who is member of the study team through the conclusion of the study.
- A crosswalk table linking the study ID to a patient identity will be destroyed within 12 months after the linked databases needed to test study hypotheses are completed.
- All electronic study data will be maintained in a computerized database residing on a username- and password-protected file server to which only the researchers involved in the study will have access.

- All study-related paper documents containing individually identifiable information will be maintained in locked file cabinets.

9.1.6 PUBLICATION AND DATA SHARING PLAN

In addition to presenting results at national meetings and in peer-reviewed journals, the investigators are available for any other dissemination activities that AHRQ staff deem appropriate. We plan to register this study on ClinicalTrials.gov and post results of the study on ClinicalTrials.gov when available, consistent with HP and EH research policies. As study findings become available, we will share with EH clinical leaders and EH Patient Advisory Councils. The importance of translating evidence-based care recommendations into primary care practice has long been known as a very high priority but few projects have addressed this need in children and adolescents living in rural regions, at risk of long-term adverse cardiovascular outcomes by virtue of elevated BP and related cardiovascular risk factors and with limited access to pediatric subspecialty care. A key deliverable of this project is identification of optimal implementation strategies for clinical decision support or other care improvement interventions in rural clinics. These findings can then be extended to improve care for other pediatric risk factors and clinical conditions, especially in rural areas. The proposed study aims to translate the billions of dollars of private and public-sector investment in EHR technology into tangible improvements in the quality of care that children and adolescents receive in primary care practices.

Sharing of study procedures and outcomes is an essential element of this research. We are determined to ensure that data sharing occurs on a local, regional and national level.

Our plan includes the following:

Local: We will work closely with clinical and administrative leaders at Essentia Health (EH) to ensure our CDS tool will be well accepted and locally relevant. During the intervention and analysis phases of the project we will continue to meet with these leaders to update them on our findings. If desired, once the intervention period is complete, we will activate the CDS at all EH pediatric and family practice clinical sites. Findings of our research will be presented to local clinical and administrative leaders.

Regional: To assure regional dissemination of results and findings of this research will be presented at regional conferences, such as the Minnesota Academy of Family Physicians Innovation and Research Forum, and others. Results will also be communicated to other regional and state-wide medical groups including the Minnesota Department of Health and the Institute for Clinical Systems Improvement, a regional shared learning quality improvement organization.

National: Our main study findings will be presented at national meetings and will be published in peer-reviewed journals. If the funding agency so desires, and if permitted under then-current law, at the conclusion of the funding period we may provide a de-identified data set to AHRQ at their written request for the use of other qualified researchers in the future.

9.2 ABBREVIATIONS AND SPECIAL TERMS

AAP	American Academy of Pediatrics
BP	Blood pressure
BMI	Body mass index
BPA	Best practice advisory
CDS	Clinical decision support
DBP	Diastolic blood pressure
EH	Essentia Health
EHR	Electronic Health Record
HP	HealthPartners
HTN	Hypertension
IRB	Institutional Review Board
LVH	Left ventricular hypertrophy
PI	Principal Investigator
QA	Quality Assurance
SAE	Serious Adverse Event
SBP	Systolic blood pressure
sIRB	Single Institutional Review Board
USPSTF	United States Preventive Services Task Force

9.3 PROTOCOL AMENDMENT HISTORY

IRB Ref. Number	IRB Submission Date	Approval Date	Description of Change
AMND-1.1	04.28.2021	06.09.2021	Request for single IRB and waiver of assent
AMND-2.0	01.07.2022	01.13.2022	Updated details for the pilot and training plan
AMND-6.0	03.16.2022	03.21.2022	Updated for full intervention (Phase 2)
AMND-7.0	01.19.2023	01.25.2023	Added data dictionary for safety and reporting
AMND-8.0	10.09.2023	10.10.2023	Updated to reflect Initial review of clinician and staff surveys
AMND-10.0	12.14.2023	12.18.2023	Added Appendix 1 describing assessment of cardiovascular risk factors and health related social needs
AMND-13.0	03.06.2025	TBD	Updated data collection dates

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11 APPENDIX 1 – ASSESSMENT OF RISK FACTORS

Assessment of Cardiometabolic Disease Risk Factors and Health-Related Social Needs in Pediatric Patients with and without IDD

Background and Rationale:

Cardiometabolic risk in childhood and adolescence is associated with future disease and cardiovascular mortality[1,2,3]. Although precise definitions and cut-offs may vary, cardiometabolic and cardiovascular disease (CVD) risk in childhood and adolescence can be measured across five domains (blood pressure (BP), lipids, glucose/Hgb A1c, smoking, body mass index (BMI)). Of these, BP and BMI are routinely assessed at all pediatric primary care visits, smoking status may be assessed during adolescent well visits, and lipids and glucose/Hgb A1c may only be assessed in patients with obesity or other risk factors[4,5,6].

People with Intellectual and Developmental Disabilities (IDD) have higher rates of cardiometabolic risk factors and cardiovascular disease compared to similar patients without IDD[7,8]. There is evidence that this risk begins to accumulate in childhood, but there is a lack of data describing the prevalence of CVD risk factors in pediatric patient populations with IDD. In order to learn how to better serve pediatric patients with IDD and their families and prolong length and quality of life for individuals with IDD, better data on risk factors and areas for potential risk modification are needed.

Essentia Health started routinely collecting data on patients' health-related social needs (HRSN) in 2020 in all primary care visits. This includes personal and medical transportation, food scarcity and food insecurity, and financial strain aimed to identify those report any adverse social conditions that can contribute to poor health[9,10,11]. Prior studies have noted an association between CVD risk and HRSN[12].

The PedsBP clinical decision support (CDS) tool has potential to improve BP measurement, remeasurement and control, as well as raise awareness of CVD risk factors and work up for secondary causes[13]. Assessment of HRSN routinely occurs in primary care clinics and association of HRSN and CVD risk factors is important to describe.

This cross-sectional analysis utilizes the baseline data from patients' PedsBP CDS index visit obtained from web service call data that is gathered at the index visit, as well as historical data prior to the index visit that will be gathered from the EHR.

Aims:

1. In youth 6-17 years of age, describe the assessment of CVD risk factor and HRSN data in the EHR by:
    a. rural vs urban dwelling
    b. male vs female sex
    c. IDD vs non-IDD
2. In youth 6-17 years of age with CVD risk factor and HRSN assessment in the EHR, describe the prevalence of CVD risk factors and HRSN:
    a. rural vs urban dwelling
    b. male vs female sex
3. Describe the association of CVD risk factors and HRSN.
4. Determine the prevalence of having one or more- cardiometabolic risk factors among a cohort of pediatric patients 6-17 years receiving care in a large, primarily rural health system with a diagnosis of IDD (as defined by

ICD-10 diagnostic codes for IDD). Compare this prevalence with that of patients of similar age in the health system without IDD diagnosis.

Hypotheses:

1. Comparing study-eligible pediatric patients on the assessment of CVD risk factor and HRSN data:
    a. Assessment of CVD risk factors and HSRN will be more complete in urban-dwelling than rural-dwelling pediatric patients.
    b. Assessment of CVD risk factors and HSRN will be more complete in female than male pediatric patients.
    c. Assessment of CVD risk factors and HSRN will be more complete in patients with IDD than patients without IDD.
2. Comparing study-eligible pediatric patients on the prevalence of CVD risk factors and HRSN:
    a. Rural pediatric patients will have a higher prevalence of CVD risk factors and HRSN than urban pediatric patients.
    b. Male pediatric patients will have a higher prevalence of CVD risk factors and HRSN than female pediatric patients.
3. Patients with a higher count of HRSN will be more likely to have any CV risk factors.
4. Among those with at least two documented cardiometabolic risk measures, those with IDD will have increased CVD risk, compared with those with no IDD diagnosis.

Population: All PedsBP study-eligible patients aged 6-17 years on the date of a potential index visit (first visit) at a randomized Essentia Health clinic between August 1, 2022, to July 31, 2023.

Exclusion Criteria: Opted out of use of their data for research prior to performing analyses.

Informed Consent: See Section 9.1.1 above.

Main Measures: A complete list of variables that will be collected can be found in the data dictionary (separate document located in the study file).

Variable	Description	Data Source
Patient Description	Age, sex, race, ethnicity, vitals, labs, medications, diagnoses, encounters	CDS, EHR Clarity
Provider Type and Specialty	Standard categories	EHR Clarity
Tobacco and Marijuana Status	Standard categories	EHR Clarity
Rural-urban commuting area (RUCA)	Ruca, zip code(s)	EHR Clarity
Intellectual and Developmental Disabilities (IDD)	Autism spectrum disorder, intellectual disability, cerebral palsy, genetic conditions, child disintegrative disorder fetal alcohol syndrome	EHR Clarity
Health-Related Social Needs (HRSN)	Personal transportation, medical transportation, food scarcity, food insecurity, and financial strain	EHR Clarity

Analysis Plan:

Aim 1: Describe the assessment of CVD risk factor and HRSN data in the EHR by urban vs. rural patient dwelling, patient sex, IDD vs. non-IDD status.

The count and percentage of patients having assessment in the EHR will be computed for: a) assessment of information needed to document each individual CVD risk factor in the EHR (e.g., BP measured at the index visit, lipids measured ever, glucose or A1c measured ever, smoking assessed in the past 2 years, BMI recorded in the past 2 years, problem list diagnosis of any CVD risk factor), b) documentation of any HRSN in the EHR. These summaries will be computed for all patients and stratified individually and multiply by patient dwelling (rural, urban), patient sex, patient age group. Differences in assessment of information (0/1) for each assessment will be assessed with logistic regression analysis predicting assessment of information from patient factors used as stratification variables.

The same analysis strategy will be used to describe and test assessment of CVD risk factor information and HRSN for patients with IDD vs. non-IDD.

Aim 2. Describe the prevalence of CVD risk factors and HRSN by urban vs. rural patient dwelling, patient sex.

The prevalence of CVD risk factors will be computed as: a) the prevalence of any risk factor among the five of interest, and b) the prevalence of each individual risk factor. HRSN prevalence will be computed as the presence of any HRSN present. These summaries will be computed for all patients having CVD risk factor assessment (and HRSN assessment) from Aim 1 and stratified individually and multiply by patient dwelling (rural, urban), patient sex, patient age group. Differences in prevalence as defined above will be assessed with logistic regression analysis predicting prevalence from patient factors used as stratification variables. In addition, multiple linear regression will be used to assess the association of count of CVD risk factors with patient factors. Models will include the stratification factors listed above.

Aim 3. Describe the association of CVD risk factors and HRSN.

The association of any CVD risk factor (0/1) with presence of HRSN (0/1) overall and stratified individually and multiply by patient dwelling, patient sex, patient age group will be assessed in contingency table analysis and tested via Pearson and Cochran-Mantel-Haenszel chi-square tests. The association of each CVD risk factor with presence of HRSN (0/1) will be addressed with the same approach.

Multiple linear regression will be used to assess the association of count of CVD risk factors with presence of HRSN (0/1). Models will include the stratification factors listed above. One set of models will exclude any interactions and a second set will include interactions in order to formally test for differences in the association of count of CVD risk factor and HRSN by subgroups (e.g., patient age group).

Aim 4. Describe the prevalence of having one or more CVD risk factors in patients with a diagnosis of IDD vs. no diagnosis.

The prevalence of CVD risk factors will be computed as: a) the prevalence of any risk factor among the five of interest, and b) the prevalence of each individual risk factor. HRSN prevalence will be computed as the presence of any HRSN present. These summaries will be computed for all patients having CVD risk factor assessment (and HRSN assessment) from Aim 1, and multiply stratified by IDD vs. non-IDD and patient age group. Differences in prevalence as defined above will be assessed with logistic regression analysis predicting prevalence from IDD vs. non-IDD and patient factors used as stratification variables. In addition, multiple linear regression will be used to assess the association of count of CVD risk factors with IDD vs. non-IDD and patient factors.

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