SPECIFIC AIMS – Project 2

Human papillomavirus (HPV) vaccination is effective and recommended to protect against six types of cancer, but HPV vaccine coverage remains low, especially in rural areas. Provider communication has a powerful influence on HPV vaccine uptake. We have demonstrated that Announcement Approach Training (AAT) effectively improves provider communication and increases HPV vaccination uptake. The AAT workshop is a 1-hour communication workshop designed to help primary care teams improve the frequency and effectiveness of provider recommendations for HPV vaccination.

A promising tool to expand the impact of AAT is clinic-level financial incentives. Policy innovation and payment reform efforts are focused on better aligning financial incentives in healthcare systems with quality of care. Many payment reforms also include insights from behavioral economics. Examples include structuring financial incentives to take advantage of loss aversion and providing peer comparison feedback on incentivized quality metrics (here, HPV vaccination rates). However, no studies have established whether financial incentives with behavioral nudges motivate providers to improve HPV vaccine communication and provision.

As part of the proposed P01 Program Project, "Improving Provider Announcement Communication Training (IMPACT)," the **overall goal of the proposed randomized clinical trial (RCT) is to test promising behavioral economic alternatives to amplify the impact of AAT** by motivating providers to apply what they learn in AAT. We propose to conduct an RCT to examine whether *clinic-level* financial incentives, with behavioral nudges, can improve HPV vaccination communication and uptake. The specific aims are as follows.

Aim 1. Characterize providers' perceptions of financial incentives with behavioral nudges tied to HPV vaccination. *Activities to reach this aim:*

a. Contribute to national survey of 2,500 primary care team members. Assess providers' perceptions of HPV vaccine-related financial incentives and behavioral nudges (e.g., prepayment contracts, peer comparison feedback).
b. Refine feedback report using electronic health record (EHR) data to calculate provider-level HPV vaccine up-to-date and initiation rates. Interview and conduct usability testing with 6-8 providers.

Aim 2. Demonstrate the impact of clinic-level financial incentives on HPV vaccine communication and uptake in healthcare systems.

a. Randomly assign 34 clinics to 1) AAT or 2) AAT plus financial incentives, with behavioral nudges, tied to clinic-level improvement in HPV vaccination rates.
b. Assess HPV vaccination uptake (up-to-date and initiation) at 6, 12, and 18 months using EHR data and whether uptake varies by rurality.
c. Examine change in provider cognitions and behavior from baseline to 12 months via provider survey.

Hypothesis: Clinic-level financial incentives and AAT increase HPV vaccine communication and uptake relative to AAT alone.

Aim 3. Generate guidance for systems to compare and implement AAT and financial incentives.

a. Assess cost per additional adolescent initiating the HPV vaccine in partnership with the Intervention Core. Share with Project 4 to support cost-effectiveness analyses.
b. Examine other implementation outcomes: acceptability, adoption, appropriateness, feasibility, fidelity, reach, and sustainability using surveys, checklists, and key informant interviews.
c. Characterize determinants of AAT and financial incentives implementation and strategies for improving HPV vaccination that providers and clinics use in response to financial incentives.
d. Contribute module to the AAT Intervention Package for improving HPV vaccination in healthcare systems.

Hypothesis: Financial incentives with AAT is cost-effective relative to AAT alone.

The proposed RCT is **significant** because it will demonstrate whether and how financial incentives improve provider communication and increase HPV vaccine uptake. The proposed research is **innovative** in adopting behavioral economic principles to improve effectiveness of pay-for-performance strategies in pediatrics. The proposed research addresses the **IMPACT Program Project theme** of amplifying the impact of a Research-Tested Intervention Program to improve HPV vaccine communication by providing much-needed evidence for the value of HPV communication interventions within healthcare systems. Ultimately, program-wide **dissemination** of research findings, the AAT Intervention Package, and related training opportunities to healthcare systems across the United States (US) will greatly improve public health by reducing the incidence of HPV and HPV cancers.

RESEARCH STRATEGY – Project 2

SIGNIFICANCE

HPV vaccination rates are far short of national goals. HPV vaccination could eliminate 32,100 cancers in the US annually, which represents over 80% of cervical and anal cancers and the majority of the other HPV cancers as well.[1] In 2006, the Advisory Committee on Immunization Practices (ACIP) recommended the routine HPV vaccination of adolescent females ages 11-12 and in 2011 extended this recommendation to adolescent males.[2,3] Although rates of HPV vaccination have increased in the US in the past decade, only 72% of adolescents aged 13-17 initiate the HPV vaccine series and just over half (54%) complete it.[3] HPV vaccination rates are lower, and incidence of HPV-associated cancers higher, in rural areas. These patterns are also evident in North Carolina, a state with a large rural population.[3] These facts, together with recent Covid-19 related delays in adolescent vaccination,[4,5] demonstrate the need for effective policies to increase HPV vaccination.

Scientific Premise

Providers and clinics within healthcare systems are a high-leverage intervention target. Adolescents whose parents receive a recommendation from a HPV vaccine provider to vaccinate their child against HPV are more likely to be vaccinated than those whose parents do not receive a provider recommendation.[6-13] Despite the critical role providers can play in the decision to vaccinate, more parents need to receive a recommendation from a provider.[7,8,12,13] Our team in the proposed P01 Program Project, "Improving Provider Announcement Communication Training (IMPACT)," have demonstrated that Announcement Approach Training (AAT) is effective at improving provider communication and increasing HPV vaccination rates.[14,15] The integrated projects of IMPACT are focusing on healthcare systems because patients increasingly receive care from providers in systems.[16] In addition, systems' policies (e.g., financial incentives) can create environments that encourage providers to improve HPV vaccine communication.

HPV vaccination is an ideal target for financial incentives. While AAT gives providers the tools to improve HPV vaccine communication, providers need to be motivated to recommend as well. Prior studies, now nearly 20 years old, have shown financial incentives increase delivery of other childhood and adult immunizations.[17-24] This success may be attributable to two features that make immunizations ideal targets for financial incentives. First, financial incentives are most effective when the incentivized behaviors are simple and easy to track.[17,18] Completion of the HPV vaccination series requires decision-making at only two or three time points per patient. These measures can be tracked using electronic health records (EHRs) that are already integrated in healthcare systems. Use of related quality measures, such as the Healthcare Effectiveness Data and Information Set (HEDIS) Immunizations for Adolescents measure, is already pervasive in healthcare systems.[25] Second, financial incentives are most effective when there is room for improvement.[18,26,27] Current rates of HPV vaccinations among adolescents fall well below the Healthy People 2020 goal of 80%.[3,28] Despite these features, the effect of provider financial incentives on *HPV vaccination* has not been evaluated.

Pay-for-performance using financial incentives is becoming widespread as alternative-payment models become more common. The US healthcare system is transitioning from one dominated by fee-for-service payments that reward high volume to a system that rewards providers who provide high-value care.[29,30] The Centers for Medicare and Medicaid Services (CMS) and other payers have begun using alternative payment models, such as pay-for-performance and financial incentives, to more closely link payment for services to quality of care.[29,31,32] Although pay-for-performance is becoming more widespread, its effect on the uptake of HPV vaccinations has not yet been established.

Behavioral nudges can enhance effectiveness of traditional pay-for-performance. Behavioral nudges create choice environments in which desired choices are easier.[33] Nudges combined with financial incentives may provide further motivation for providers to provide high-value preventive care.[34-36] For example, the impact of a financial incentive framed as a loss may be larger than the impact of a financial incentive of the same size that is framed as a gain.[34,37] Although loss aversion has been demonstrated in consumers and patients, our trial will be one of few to integrate it into provider incentive programs.[34] Meeting goals to receive an incentive requires regular feedback, which can also incorporate behavioral nudges.[38-40] Peer comparison feedback, in which providers' performance is ranked amongst other providers in the clinic, motivates improved performance by engaging professional pride, a desire for social esteem, and establishing social norms. As a component of team-based incentives, peer comparisons can create positive peer effects within a group.[34]

Why is this randomized clinical trial (RCT) needed? We will conduct an RCT to examine whether financial incentives tied to clinic-level improvement in HPV vaccination rates can improve HPV vaccine communication and uptake. The RCT is needed for several reasons. First, this RCT will provide the first estimate of the effect of provider financial incentives on the initiation and completion of HPV vaccination. The evidence from this RCT aligns with current emphasis on value-based payment in the US healthcare system, which increases momentum for adoption of HPV vaccination. Second, this RCT will use behavioral nudges as part of the financial incentives package. Behavioral nudges are one of the few consistently effective strategies for vaccination[41] and have been shown to be cost-effective for consumer and patient behaviors; however, little is known about their effect among healthcare providers. Third, this RCT will examine how the effectiveness of financial incentives could vary by rurality. Clinics that primarily serve patients who live in rural areas are different from non-rural clinics in many dimensions that could affect their ability to respond to the incentives (e.g., lower EHR adoption rates, patient mix). Finally, as healthcare systems choose among interventions to increase HPV vaccine uptake, they consider an intervention's cost-effectiveness; how it will be received (e.g., acceptability, appropriateness); and whether it can be integrated into practice (e.g., feasibility, fidelity, sustainability). Furthermore, they need information about potential implementation facilitators and barriers to ensure the success and longevity of new initiatives. The Intervention Core will synthesize evidence created across research projects in the IMPACT Program into the **AAT Intervention Package**, a resource for healthcare systems and public health agencies to promote better HPV vaccine communication. This much-needed evidence will greatly improve public health by reducing the incidence of HPV and HPV-associated cancers.

INNOVATION

This RCT will provide causal evidence on clinic-level financial incentives for HPV vaccination. Despite the growing body of evidence for pay-for-performance arrangements that tie financial incentives to the quality of care,[17,18,26,27,42] no trial-based evidence exists for the effect of clinic-level financial incentives on increasing HPV vaccination. The existing evidence for clinic-level financial incentives relates to childhood vaccines and is nearly 20 years old.[19,20,23,24] That literature showed that clinic-level financial incentives were effective at increasing childhood vaccination rates. The literature on financial incentives for HPV vaccination has focused on patient-level incentives and has shown small, positive effects on the likelihood of adolescents being vaccinated.[43] For the reasons noted above, we believe that HPV vaccination is an ideal context for evaluating the effectiveness of clinic-level financial incentives. *This RCT will estimate the causal effect of clinic-level financial incentives on HPV vaccination rates, thereby delivering information needed by scientists, payers and healthcare systems looking for strategies to increase HPV vaccination rates.*

This RCT adopts behavioral economic principles to improve effectiveness of pay-for-performance strategies. Behavioral economics has provided several insights into cognitive biases that can be leveraged to "nudge" choices towards socially desirable outcomes.[33] Some of these are beginning to be incorporated into pay-for-performance schemes. For example, Comprehensive Primary Care Plus, a national program from CMS, uses commitment contracts in which quality-based incentives are paid up front and providers are at the risk of losing the payments if quality targets are not met.[44] This approach takes advantage of loss aversion, in which more effort is given to avoid losses than to achieve a similarly sized gain.[34,37] Similarly, many public programs have taken advantage of people's natural proclivity for social comparison to incent pro-social behaviors using positive peer pressure.[45-48] The RCT design will use the concepts of loss aversion and social comparison: peer comparison feedback with clinic-level, pre-paid financial incentives. *This RCT will use behavioral economic strategies to maximize the impact of the tested interventions to increase HPV vaccination.*

This RCT contributes to the scant literature on cost-effectiveness for HPV vaccine-focused interventions. There are relatively few evidence-based interventions to increase HPV vaccination, and the majority of those do not have evidence of their cost-effectiveness. For example, the National Cancer Institute (NCI) lists six programs addressing HPV vaccination in their Research-Tested Intervention Programs.[49] Of those, only one program has published evidence of its cost-effectiveness.[50] Our proposed RCT will collect intervention cost data, report cost per additional adolescent initiating for the tested intervention, and share this information with Project 4 where it will be combined with data from interventions tested in other Projects via simulation modeling. *In doing so, this Project will generate knowledge about the value of HPV vaccination interventions that is needed by public health vaccination programs, payers, and healthcare systems.*

APPROACH

Research Team

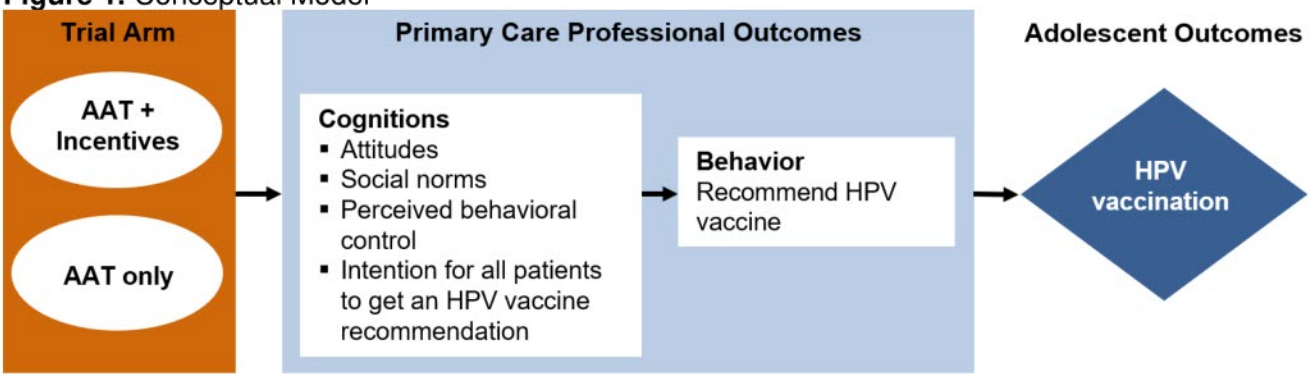
We have assembled a team whose expertise in health economics, behavioral economics, pediatrics, RCTs, implementation science, and health services research is required for a successful trial. **Dr. Justin Trogdon** (Project Lead) is a health economist and Director for Cancer Health Economics Initiatives for the Cancer Outcomes Research Program of the University of North Carolina (UNC) Lineberger Comprehensive Cancer Center. He has been a Principal Investigator on 16 funded research grants and contracts totaling nearly $12 million in total costs, including two R01 awards. His HPV vaccine research includes geospatial analysis of HPV vaccination patterns and vaccine providers, time series estimates of the effects of the release of the latest version of HPV vaccine on vaccination coverage, analysis of claims and survey data to assess the effects of state-level policies on HPV vaccination, and costing and cost-effectiveness modelling of interventions to increase HPV vaccination.[51-56] **Dr. Harsha Thirumurthy** is a health economist and the Associate Director at the University of Pennsylvania Center for Health Incentives & Behavioral Economics. He has been the Principal Investigator on multiple R01 RCTs testing behavioral interventions, including financial incentives and peer referrals, to improve health behaviors. **Dr. Michelle Hernandez** is a pediatrician at UNC Healthcare and an Associate Professor of Pediatrics at UNC School of Medicine. She serves as the Pediatric and Adolescent Director at NCnet, a practice-based research network at UNC (see Setting below), and will lead recruitment. **Dr. Sarah Birken** is an implementation scientist at Wake Forest University and will advise on Aim 3 analyses. Our team will also have access to experts in RCTs (**Drs. Noel Brewer**, **Stephanie Wheeler**, and **Joseph Ibrahim**), biostatisticians (**Dr. Ibrahim**), and implementation scientists (**Dr. Bryan Weiner**) through the Cores.

Connected Health Applications and Interventions (CHAI) Core (www.chaicore.com) is a National Institutes of Health-funded core facility through the UNC Gillings School of Global Public Health and the Lineberger Comprehensive Cancer Center. CHAI Core has extensive experience in qualitative research and graphic design, including designing personalized feedback via text, email, and app notification. CHAI Core has provided research support and design services to over 130 projects, including multiple RCTs. CHAI Core will lead refinement of the peer comparison feedback report (Activity 1c) and qualitative research (Activity 3c).

Conceptual Model

Our RCT is guided by the **Theory of Planned Behavior** as the core model to understand how our intervention works to change provider recommendation behavior (Figure 1).[57] In the context of our intervention, the theory suggests that intervening to improve *cognitions*, through financial incentives that change attitudes, establish new social norms, and increase perceived behavioral control and intentions to recommend will change HPV vaccine recommendation *behavior*. The resulting increase in provider recommendations will lead to increases in HPV vaccination among adolescents.

Figure 1. Conceptual Model



Two theoretical frameworks describe how the *implementation* of the interventions affect outcomes. **Proctor et al.'s Implementation Outcomes Framework**[58] suggests that our intervention should be well received (e.g., acceptable, appropriate) and integrated into practice (e.g., feasible, sustainable). Furthermore, the intervention should be delivered with fidelity, reach most patients with provider recommendations, and be made at a reasonable cost to sustain impact over time. The **Consolidated Framework for Implementation Research**[59] (CFIR) informs our understanding of determinants of AAT and financial incentives implementation (e.g., clinics' structural characteristics; rurality of the patient population served).

Setting

Our primary clinical partner will be the NCnet practice-based research network at UNC. North Carolina has a substantial rural population (34%) and HPV prevention needs typical of the US overall.[3] NCnet includes 159 pediatric and family medicine clinics across North Carolina, such as the UNC Physician's Network with over 90 clinics across the state. Nearly all clinics in NCnet use a common EHR (Epic), which will create efficiencies in implementing the peer comparison feedback report in Aim 1. In addition, our research team can access EHR records for NCnet clinics that are part of the UNC system via the Carolina Data Warehouse for Health, a research ready EHR database. NCnet staff have extensive experience in working with investigators and community-based clinics to conduct pragmatic trials, which will be critical to enhance feasibility and recruitment of clinics.[60,61] If we subsequently need a larger pool of clinics, NCnet is a member of the larger practice-based research network North Carolina Network Consortium. The North Carolina Network Consortium includes 67 additional clinics in North Carolina affiliated with other healthcare systems using Epic and can also serve as a source of clinics.

Preliminary Evidence

We identified 36 family medicine and pediatric clinics in the Carolina Data Warehouse for Health. Using EHR data for adolescent patients who visited each clinic between 2017 and 2018, we calculated the proportions of 11-12 and 13-year-old patients, respectively, who had initiated (at least one dose) and completed (two doses) the HPV vaccine series. Rates of HPV vaccine initiation and completion were low and heterogeneous across clinics, with high-performing clinics initiating the vaccine in over three-quarters of 13-year-old patients and low-performing clinics initiating the vaccine in less than a third (**Table 1**).

We also conducted semi-structured interviews with one provider and one clinic manager from eight clinics affiliated with NCnet (16 interviews). The interviews explored participants' opinions on financial incentives for HPV vaccination. Participants agreed reporting on HPV vaccination was feasible in their EHR, but few currently reported on HPV vaccinations specifically. Epic has recently been integrated with the state immunization information system to provide full vaccination history for all patients. One provider lamented, "*Sadly, because HPV rates are not one of the measures we are incentivized for, we don't have that information handed to us.*" In general, both providers and practices managers felt that publishing and routinely sharing HPV vaccination rates across providers would have a positive impact on increasing HPV vaccination rates at their clinic.

Regarding financial incentives, all participants had experience with pay-for-performance arrangements for other metrics. In general, most participants felt financial incentives had been effective in helping the clinic meet their quality metrics. According to one provider: "*If HPV vaccine became a quality metric with a financial incentive connected to it, then you would see rates go up very quickly.*"

Table 1. Preliminary Evidence on HPV Vaccine Coverage at UNC Clinics

Characteristic, mean ± SD	N=36
# providers per clinic	7.3 ± (5.6)
Min, max	2, 29
11-12 year olds	
# patients per clinic	275 ± (253)
Min, max	51, 823
Initiated (%)	43.7 ± (16.0)
Min, max (IQR)	10.5, 79.2 (18.5)
Completed (%)	20.5 ± (11.3)
Min, max (IQR)	1.9, 49.8 (12.1)
13 year olds	
# per clinic	166 ± (148)
Min, max	27, 507
Initiated (%)	52.1 ± (16.5)
Min, max (IQR)	20.8, 85.3 (26.1)
Completed (%)	32.5 ± (18.1)
Min, max (IQR)	3.2, 81.6 (24.4)

Aim 1. Characterize providers' perceptions of financial incentives with behavioral nudges tied to HPV vaccination.

In **Activity 1a**, we will contribute to the national primary care team survey to understand their current experiences with, and preferred designs for, financial incentives with behavioral nudges (e.g., prepayment contracts, peer comparison feedback). In **Activity 1b**, we will refine a feedback report to assess HPV vaccination rates using EHR data from the clinics participating in the Aim 2 RCT to ensure providers can track progress on incentivized HPV vaccination metrics. ***Aim 1*** *will generate new national findings on opportunities for expanding financial incentives with behavioral nudges for HPV vaccination.*

1a. National survey

The first activity of this aim is to contribute to the development and analysis of the national primary care team survey, which will be shared by three IMPACT projects. The primary goal of the national survey is to fill significant knowledge gaps in implementation of financial incentives for HPV vaccination. For Project 2, we seek to understand providers' experience with, and perceptions of, performance-based incentives and behavioral nudges. The secondary goal of the national survey is to inform refinements to the projects' communication interventions. Together with our pilot qualitative interviews and usability testing with local providers (described below), the national survey will allow us to consider implementation challenges faced by providers in other regions of the country and serving in diverse vaccination roles.

The Data Core will manage the national survey, including the subcontractor WebMD, and IMPACT projects will contribute items to address their own aims. This section will focus on Project 2's contribution to the survey. Overall details about the national survey can be found in the Data Core research strategy.

Participants and recruitment. Survey participants will be a national sample of 2,500 primary care team members, consisting of 1,500 HPV vaccine providers (physicians, physician assistants, and nurse practitioners) and 1,000 registered nurses and medical assistants. Health professionals of all sexes will be included with self-reported sex collected in the survey.

Measures. The national survey will inform six research questions for Project 2 (**Table 2**). It will assess providers' experiences with financial incentives and behavioral nudges, including their perceived effectiveness of each, which will provide valuable information about the prevalence of these strategies in pediatric and family medicine clinics nationwide. The information from the national survey will also help design the feedback report used in the RCT to maximize acceptability and actionability.

Procedures. Project 2 will pilot test each of its own measures. We will first solicit the help of our Clinical Advisory Board to assess our questionnaire's face validity. Next, we will cognitively test the items with eight local providers in NCnet to ensure readability and comprehension. Together with the Data Core and other projects, we will review WebMD's electronic survey for errors and readability. We will also review the results of WebMD's survey pilot to check for appropriate skip patterns and distribution of response items.

Table 2. Project 2 Research Questions Addressed in the National Survey

Question
How are immunization rates shared at the provider level? At the clinic level?
What do providers think of the idea of routinely sharing HPV vaccine rates across providers within their clinic?
Does clinic participate in any "pay-for-performance" initiatives? If so, are vaccinations included? HPV vaccine?
What other kind of clinic-level financial incentives (e.g., bonuses or penalties) exist at the clinic? Do any include HPV vaccination goals?
How have these rewards/recognitions been viewed by providers at the clinic?
How (in)effective have existing financial incentives been?

Analyses. We will describe the types of primary care team members (e.g., physicians, nurse practitioners) likely to have experience with financial incentives and behavioral nudges. We will estimate separate regression models with items for the questions in **Table 2** as the dependent variables. As clinics that primarily serve patients who live in rural areas are different from non-rural clinics in many dimensions that could affect their ability to respond to the incentives (e.g., lower EHR adoption rates, patient mix), the explanatory variables will include provider demographics collected in the national survey (e.g., rurality of clinic). Regression models will use appropriate functional forms for each item scale (e.g., logit for 0/1 outcomes).

1b. Refine feedback report using EHR data to calculate HPV vaccination rates

To ensure that providers can track progress on incentivized HPV vaccination, we will provide a feedback report. The feedback report, based on our team's AAT clinic-level report card and refined by CHAI Core, will incorporate recommendations from four sources: survey responses from the national survey in Activity 1a, IMPACT's Clinical Advisory Board, systematic reviews of feedback in a broad range of healthcare settings,[62-65] and best practices from user-centered design.[66] The report will use the behavioral nudge of peer comparison. Providers' rates will be reported relative to 1) other providers in the clinic (e.g., percentile rank), 2) overall clinic rates, and 3) clinic-level quality improvement targets (e.g., percent improvement from baseline). The report will be delivered via email monthly to providers and discussed during monthly in-person staff meetings. The report will be designed for easy comprehension. Furthermore, we will track the rate at which providers are engaging the report website to measure reach of the feedback.

Data source. For development, we will use the Carolina Data Warehouse, derived from the Epic EHR, which will be used by most participating clinics in the RCT. All patients ages 9 to 17 years of age who visited a participating clinic at least once within the prior two years will be included. Patients will be attributed to providers using a plurality algorithm – patients will be attributed to the most frequently visited provider in the prior two years. In the case of ties, we will attribute the patient to the most recent provider.

Procedures. We will search for HPV vaccinations in procedures and immunization records. HPV vaccination procedures delivered in the healthcare system will be identified using Current Procedural Terminology codes for the nonavalent (90651) vaccine, which is exclusively used in North Carolina. We will then search the EHR for patients' history of immunization records, which have recently been linked to the state's immunization information system, to identify vaccinations administered previously or outside of the healthcare system.

Measures. For each provider, we will calculate up-to-date HPV vaccination, defined by current HEDIS measures[25] as the proportion of the provider's attributed patients who turn 13 years old during the measurement year with at least two HPV vaccines with different dates of service on or between the patient's 9th and 13th birthdays, with at least 146 days between the first and second dose of the HPV vaccine, OR at least three HPV vaccines with different dates of service on or between the patient's 9th and 13th birthdays. This is the primary measure because it is the HPV-related component of the quality metric most healthcare systems are using for quality improvement and reporting standards.[25] We will also include initiation (first dose) rates among ages 11-12 and providers' patient panel size, which is important for metric stability.

Analysis. Once we have an initial draft report, we will interview and conduct a usability test with six to eight providers from our pilot qualitative interviews. CHAI Core will lead this task as well given their subject matter expertise and experience in user-centered design. Suggested changes will be incorporated into the report. **The result of Aim 1 will be an engaging tool to monitor HPV vaccination rates at the provider and clinic levels, which will be incorporated into the Program Project's AAT Intervention Package.**

Aim 2. Demonstrate the impact of clinic-level financial incentives on HPV vaccine communication and uptake in healthcare systems.

In this aim, we will conduct a cluster RCT to compare the effectiveness of AAT with clinic-level financial incentives versus AAT alone. AAT is an NCI-designated Research-Tested Intervention Program that instructs providers to use a presumptive announcement.[14] In **Activity 2a**, we will randomize 34 clinics (17 per arm) in a 1:1 ratio to each arm. In **Activity 2b**, we will assess the impact of each intervention arm on the change in HPV vaccine up-to-date and HPV vaccine initiation rates at 6, 12 and 18 months. Finally, in **Activity 2c** we will examine the change in the intermediate outcomes (cognitions and behavior) attributed to AAT via a survey of providers. ***Aim 2*** *will provide gold-standard, causal evidence for new interventions aimed at improving provider communication and increasing HPV vaccine uptake, which will reduce HPV-associated cancers.*

2a. Recruit and randomize clinics

Participants and recruitment. Thirty-four clinics will be recruited from NCnet. Clinics must meet the following inclusion criteria: 1) specialize in pediatric or family medicine, 2) have 50 or more patients ages 11-12 in the previous two years, and 3) have at least two HPV vaccine providers who provided HPV vaccine in the previous two years. Clinics will be ineligible for the RCT if they had received AAT in the previous six months or planned to do so over the next six months, already have financial incentives *specifically* for HPV vaccination, or are already above 80% up-to-date HPV vaccination coverage on the HEDIS measure.

Following Institutional Review Board (IRB) approval, Dr. Hernandez will lead recruitment efforts using past NCnet relationships and proven processes. The processes include engaging system leadership first, a focus on clinic workflow, on-site visits by Drs. Hernandez and Trogdon, and adequate participation incentives (distinct from financial incentives tied to HPV vaccination coverage in the intervention arm only). Participating clinics will receive $2000 each, $1000 upon completion of baseline data collection and $1000 upon completion of final data collection. Clinics will be recruited in two phases, half in Year 2 and half in Year 3 so that processes can be adapted in the second phase. For each participating clinic, we will identify one or two key contacts for the project with whom the research study has primary communication.

Most NCnet clinics will be part of the same healthcare system. Recruiting and randomizing clinics within a system has several advantages. First, a common EHR will expedite data collection. Second, clinics within a system may have fewer unobserved differences across intervention arms due to shared management. Finally, working with healthcare systems provides a natural audience for implementation of successful interventions.

The challenge of randomizing clinics is the risk of contamination across arms. We believe the risks are minimal for our intervention. The intervention of financial incentives will be restricted to clinics in the intervention arm. Clinics in both arms will receive AAT. It is possible that clinic-level process changes adopted in response to the incentives in the intervention arm could be shared with the control arm. We will ask about this in our qualitative interviews in Activity 3c. To the extent contamination happens, it will only serve to minimize differences between the control and intervention arms and make our estimates conservative.

Randomization. After recruitment, clinics will be randomly assigned to one of two arms. Clinics in the first arm will receive AAT (control).[14] Clinics in the second arm will receive the same AAT and financial incentives with behavioral nudges (intervention). Clinics in the control arm will be waitlisted to transition to the intervention, which will run for an additional 12 months after the RCT. The waitlist control will increase acceptance within healthcare systems and avoid negative reactions in the control clinics. Randomization will be conducted by a biostatistician in the Data Core not affiliated with this trial.

Clinics will be assigned in a 1:1 proportion to the arms, stratified by the rurality of patients served and baseline HPV vaccination rates to ensure balance in these dimensions across arms. Rurality will be determined by Rural-Urban Continuum Codes (RUCC) of patients' home counties using addresses from the EHR.[67] Patients' counties will be defined as either metro counties (RUCC=1, 2 or 3) or nonmetro counties (RUCC greater than 3). Clinics that serve more patients who reside in nonmetro counties than the statewide average (i.e., >40% of patients' counties are nonmetro) will be considered rural clinics for this RCT. At least 25% of participating clinics overall will be rural. Using EHR data, we will calculate baseline clinic-level up-to-date HPV vaccination rates using the HEDIS definition for patients visiting the clinic in the two years ending prior to recruitment. Stratification will target an equal proportion of clinics in each arm above and below the median HPV vaccination rate at baseline. We will register our trial with ClinicalTrials.gov.

Announcement Approach Training. Clinics in both arms will receive AAT, a NCI-designated Research-Tested Intervention Program.[14,15,49,68] AAT instructs providers to use a presumptive announcement, in which the provider begins by stating the child is due for vaccines that prevent three diseases, placing HPV cancers in the middle of the list, assuming the family is ready to vaccinate.[14] If patients have questions or concerns, AAT provides skills for talking with hesitant parents, including research-tested messages for hesitant parents. The AAT workshop is one hour, in-clinic and provides continuing medical education credit for attendees. Intervention delivery will occur in spring to take advantage of summer peaks in adolescent vaccination.[69]

Financial Incentives. Clinics in the intervention arm will be eligible to receive clinic-level financial incentives if they meet pre-determined targets for HPV vaccination rates. The design of the financial incentives will incorporate best practices from the literature (**Table 3**).

Table 3. Best Practices from Financial Incentives Literature

Best Practice	Adaptation for RCT
Specific and easy to track incentive behaviors[17,18]	HPV vaccines delivered are recorded in EHR
Measures are amenable to change[18]	HPV vaccination rates have room to increase dramatically
Process measures rather than outcome measures as targets[18,27]	Vaccine delivery is process measure (rather than cancers avoided)
Room for improvement from baseline[18,26]	Clinics well below Healthy People 2020 targets of 80% (Table 1)
Directed at individuals or small teams[18,27]	Clinic-level incentives rather than at the healthcare system level
Absolute targets rather than relative targets[18]	Healthy People 2020 target (80% completion), with staged incentive the closer clinics come to meeting target
Designed in collaboration with providers and other stakeholders[18,27]	Semi-structured pilot interviews, national survey, Clinical Advisory Board
Incentives are clearly communicated to providers[17,70]	Introduced during AAT and re-iterated in monthly feedback
Positive, rather than competitive, approach[27]	Clinic-level targets provide incentives to cooperate
Uniform structure across different payers[27]	Financial incentives based on patients from all payers
Consider dominant payment structure in place[27]	Clinic-level incentive on top of base fee-for-service reimbursement and any existing provider-level quality bonuses
Estimate long-term effects even after incentive is withdrawn[17]	Analysis of HPV outcomes in the six months following removal of incentives
Support for incentive program among medical leadership[17]	Assess inner context for implementation determinants

Financial incentives that are too small will not be effective but incentives that are too large are inefficient and may crowd out intrinsic motivation to improve.[71] Evidence suggests a dose-response relationship between incentive size and quality of care outcomes.[72] Therefore, our financial incentives can still be effective in the presence of existing pay-for-performance schemes. Our incentive sizes will be guided by formative interviews with providers and clinic managers in North Carolina, the national survey, and prior literature.[19,20,23,72] We propose three sizes of incentives for tiered goals met by the clinic (**Table 4**). The clinic-level incentives will be scaled to equal $1000 per provider, but aggregated and paid to the *clinic*, for reaching the highest tier, an absolute goal of 80% of patients meeting the HEDIS up-to-date measure. Including the Healthy People 2020 goal in the incentive structure ensures clinics know the long-term goal. To keep incentives salient for clinics well below 80%, we will provide smaller bonuses for improvements relative to baseline. Based on our pilot interviews, we will let clinics distribute the incentives as they wish among healthcare professionals and staff.

Our incentives have three key behavioral nudges. First, they are team-based with clinic-level targets. Team-based incentives create additional incentives for physicians and other healthcare providers within a clinic to cooperate and work together to achieve the HPV vaccination goal.[73] Second, our financial incentives will be structured as a commitment contract, in which an up-front payment is made to a study-held account earmarked for the clinic but is at a risk of loss if the improvement targets are not met. The clinic's account balance and projected loss (if any) will be included in the monthly feedback to increase salience. Payments will be made 12 months after the start of the trial. This design is intended to take advantage of the behavioral bias of loss aversion or the endowment effect, in which people exert more effort to avoid a loss than to achieve a similarly-sized gain.[34,37] Finally, providers in the intervention arm will receive monthly, automated provider feedback of each providers' HPV vaccination rates relative to other providers in the clinic. Peer comparison is intended to motivate providers to improve for social esteem.

Table 4. Example Incentives for Average Clinic with Six Providers

Clinic HPV Target	Clinic Bonus
HEDIS ≥ 80%	$6,000
HEDIS < 80% with ≥ 10% improvement	$2,500
HEDIS < 80% with ≥ 5% improvement	$1,500

2b. Assess HPV vaccination uptake

Procedures. Clinics will participate in the RCT for one year. AAT will take place in the first quarter of the intervention year. The provider-level feedback and incentive interventions will be active for 12 months.

Measures. We will measure the HPV vaccination outcomes in the EHR for the 12-month periods ending 0 months (baseline), 6 months (preliminary), 12 months (post-intervention), and 18 months (long-run to assess outcomes after removal of incentives) after the start of the intervention. All measures will be calculated among all patients who visited a participating clinic during the study period. The primary outcome measure will be up-to-date HPV vaccination as defined by current HEDIS measures (i.e., among adolescents who turned 13 in the prior 12 months; Activity 1b). The secondary outcomes will be HPV vaccine initiation (first dose) and completion rates (two doses) among patients who turned 11 and 12 in the prior 12 months (recommended ages for the vaccine according to ACIP) and patients who turned 13 to 17 in the prior 12 months (**Table 5**). We will also measure the following covariates at the clinic-level from the EHR, trial participant survey (Activity 2c), and public sources: sex mix of patients, mix of patients residing in rural and non-rural areas, rural/non-rural location of the clinic, total number of patients ages 11-12 and 13-17, payer mix, number of providers, history of HPV quality improvement activities, ownership structure, and patient-centered medical home status. The trial participant survey will also collect provider specialty and years of experience.

Table 5. Long-Term Outcome Measures from EHR

Measure	Description
Primary: HPV vaccine completion (HEDIS)	Up-to-date at age 13
Secondary: HPV vaccine initiation, 11-12 years and 13-17 years	At least one dose
Secondary: HPV vaccine completion, 11-12 years and 13-17 years	Two doses

Analyses. We hypothesize that the addition of financial incentives to AAT will increase HPV vaccination relative to AAT alone. For all analyses, analysts will be blinded to each clinic's arm.

Inferential Analyses. The main analysis will be intent-to-treat, retaining outcomes for clinics that disenroll from the trial for any reason during the intervention. We will estimate a generalized estimating equation (GEE) model for HPV vaccination using patient-level data from the EHR (0=not up-to-date, 1=up-to-date). Using a sample of patients not yet up-to-date at baseline who visited the clinic during the study period, the GEE model will account for patients clustered by clinic. We will use a binomial link and logit family. The main effect will be

an indicator for intervention arm (at the clinic level). The coefficient represents the difference in the log odds of HPV vaccination at follow-up across the intervention and control arms. We will also adjust for baseline covariates listed above. This analysis will provide an estimate of the effect of financial incentives on HPV vaccination rates. We will repeat these analyses separately for each time point (6-, 12-, and 18-month follow up) and HPV vaccine outcome (**Table 5**). When initiation is the dependent variable, the sample will include patient not yet vaccinated who visited the clinic during the study period.

Exploratory Analyses. Several clinic characteristics could moderate the effect of the intervention. First, clinics that primarily serve patients who live in rural areas are different from clinics that primarily serve patients who live in non-rural areas in many dimensions that could affect their ability to respond to information provided in the feedback and the financial incentives. *Project 4 will provide valuable information from their first aim in the development phase of our project about key differences in rural and non-rural clinics with respect to HPV vaccination.* Second, clinics with higher baseline HPV vaccination rates have less room to improve. Conversely, clinics with higher baseline rates (but not yet at target) may have higher capability to implement quality improvement initiatives. Finally, the interventions can differ in their impact based on the number of providers in the clinic. Providers in smaller clinics may find it easier to cooperate, harder to "free ride" on others, and to share information and tactics. To test for moderating effects of the interventions, we will repeat the GEE models described above adding interactions of the intervention arm variable with each of the following clinic-level variables: rural/non-rural mix of patients, baseline HPV rates, number of providers, and sex as a biological variable.

Statistical Power. Assuming 17 clinics in each arm, 112 13-year old patients per clinic not up-to-date on average (Table 1), a 15 percentage point increase in the control arm (secular trend + AAT),[14] and a intraclass correlation of 0.033 (author calculations from AAT studies), we will have 80% power to detect a minimum of an 8 percentage point difference in our primary outcome in two-sided tests at a 95% confidence level. This effect size is similar to that found in earlier studies of provider incentives for other vaccinations,[19-22] some of which detected effect sizes up to 19 percentage points.[19]

2c. Examine change in provider cognitions and behavior

Procedures. We will survey all providers in participating clinics (n=~204) at baseline (immediately before the AAT workshop, T0), immediately after the AAT workshop (T1), and at the end of the intervention 12 months later (T2). We will use paper surveys for T0 and T1 and web-based RedCap surveys for T2. We will email a link to the survey, sending up to six email and phone reminders. Providers will receive $100 to complete T0 and T1 and $100 to complete T2.

Measures. **Table 6** describes the measures for the intermediate outcomes that will be included in the trial participant survey at all time points (T0, T1 and T2). We will measure each domain from the conceptual model for cognitions and behaviors using a single item with a 5-point Likert scale response. Items for cognitions were developed by IMPACT team members and used in the original evaluation of the AAT.[14] We will also include an item to capture providers' perceptions of the effectiveness of incentives in changing their behavior (T2).

Table 6. Selected Intermediate Outcomes from Trial Participant Survey

Measure	Description
Cognitions	
Attitudes	It is important to me that my patients get a recommendation for HPV vaccine before age 13.
Social norms	It is the norm for our team to routinely recommend HPV vaccine for patients before age 13.
Perceived behavioral control	I feel confident our team can recommend HPV vaccine effectively for our adolescent patients.
Intention to recommend	I intend to make sure all patients get an HPV vaccine recommendation before they turn 13.
Behavior: Use of presumptive announcements	When I first talk about HPV vaccine, I use language that assumes parents are ready to vaccinate.

Analyses. We hypothesize that financial incentives with AAT will improve cognitions and behavior relative to AAT alone. The proposed mechanism is that financial incentives improve *cognitions* through changing attitudes, establishing new social norms, and increasing intentions to recommend, which will change HPV vaccine recommendation *behavior*. We will estimate two-level (provider and clinic) generalized linear mixed-level regression models with a log link and Poisson family. The main effects will be an indicator for time (pre vs post), an indicator for intervention arm (at the clinic level) and an interaction of time and intervention arm. Models will include random effects for clinics and will adjust for baseline covariates listed above.

Integration. Project 4 will provide a spreadsheet to gather these effectiveness data in a standard format to support cost-effectiveness modelling. We will work with the Data Core to complete the spreadsheet and share it with Project 4. **The result of Aim 2 will be an estimate of the impact of clinic-level financial incentives on HPV vaccine communication and HPV vaccine uptake.**

Aim 3. Generate guidance for systems to compare and implement AAT and financial incentives.

In this aim, we will use sequential, explanatory mixed methods to evaluate implementation determinants and outcomes to support healthcare system's adoption and implementation of AAT and financial incentives to increase HPV vaccine uptake. In **Activity 3a,** we will assess the incremental cost of implementing financial incentives, including cost per additional adolescent initiating the HPV vaccine because of financial incentives. In **Activity 3b,** we will examine other implementation outcomes from the Proctor framework to capture how AAT and financial incentives were received (i.e., acceptability, appropriateness) and integrated into practice (i.e., adoption, feasibility, fidelity, reach, sustainability).[58] In **Activity 3c**, we will characterize determinants of AAT and financial incentives implementation from CFIR. Because the financial incentives tested are not prescriptive and allow clinics to tailor their own processes, we will also summarize the strategies clinics used for improving HPV vaccination in response to financial incentives.[59] Finally, in **Activity 3d,** we will use findings from Activities 3a-c to contribute a module to the AAT Intervention Package for improving HPV vaccination in healthcare systems. ***Aim 3*** *will support AAT and financial incentives implementation among clinics and payers.*

Participants. All providers in participating clinics (n~=204) will complete the trial participant survey (see Activity 2c). We will also recruit a purposive sample of two providers and one clinic manager from intervention clinics for semi-structured interviews.

Procedures. Implementation determinants and outcomes will be collected from three sources: study team documentation (intervention expense records, tracking logs and content checklists), participant survey, and semi-structured interviews (**Table 7**).[74] Interviews will be conducted with clinics until we reach theme saturation regarding implementation determinants and outcomes. An experienced interviewer from the CHAI core will conduct 25-30 minute, semi-structured interviews over the phone in a private room. We will develop standardized interview guides with a detailed script regarding implementation determinants and strategies. Open-ended probes will allow stakeholders the opportunity to answer questions in their own way and follow-up probes will clarify answers from stakeholders. All interviews will be digitally audio-recorded and professionally transcribed. Personal identifiers will be removed.

Table 7. Data sources for implementation outcomes

Data source	AAT	Incentives and Use of AA
Intervention expense records Facilitator time, travel, materials	Cost	Cost
Tracking logs of participants 1/clinic, 34 total	Cost, reach	
Checklists of content 1/workshop, 34 total	Cost, fidelity	
Survey of participants ~204 total	Acceptability	All outcomes
Key informant interviews 3/clinic, ~27 total	All outcomes	All outcomes

Note. AA = Announcement Approach. All outcomes = acceptability, adoption, appropriateness, cost, feasibility, fidelity, reach, sustainability.[58]

3a. Assess cost per additional adolescent initiating the HPV vaccine

Measures. Primary measures are the incremental cost of delivering the intervention and incremental cost per additional initiation due to the intervention—from the perspective of a healthcare facility or system. Secondary measures will separate fixed, start-up costs from ongoing variable costs. We will collect micro-cost data for each component of the intervention: AAT, financial incentives, and changes in the use of the announcement approach (AA). We will not assess fixed costs common to both the interventions and the "status quo" (e.g. clinic operation overhead), or costs related to the trial alone (e.g. data collection).

AAT: Facilitators will complete 2-3 minute, online time logs to the nearest quarter hour and travel and intervention materials expense logs. Logs will be completed after each AAT workshop and include practice, planning, preparation, facilitating AAT, and related tasks. Attendance logs will provide the number of provider hours spent in attending the AAT, which will be valued using median salaries by job title for the U.S.[75] **Incentives:** Study records will track the amount of incentives paid to clinics. We will also ask clinic leaders about any administrative costs to integrate incentives with existing systems (e.g., EHR modifications) in the semi-structure interviews. **Use of AA:** Providers will report typical HPV vaccine delivery time on the T0 and T2

participant surveys (see Activity 2c). They will report average time spent on HPV vaccine recommendations and documentation for their last five patients ages 11-12.

Analyses. We will calculate mean, median, and standard deviation for cost per arm per clinic and separately for fixed and variable cost per arm per clinic. We will use t-tests to compare mean costs per clinic between intervention arms. We will then calculate the difference in mean costs between intervention arms and divide by the difference in adolescents ages 11-12 initiating the HPV vaccine to estimate cost per additional initiated due to the intervention. In secondary analyses, we will examine potential economies of scale by plotting average cost per clinic against clinic size.

Integration. With the help of the Intervention Core, we will share standardized cost tables with Project 4.

3b. Examine other implementation outcomes

Measures. We will use instruments with established validity and reliability and cognitively test new items with our Clinical Advisory Board.[14,74,76] **AAT**: We will quantitatively assess the following implementation outcomes for the AAT workshops. Participant surveys T0 and T1 will ask about *acceptability* (satisfaction with the intervention activities). We expect acceptability to be above 90%, based on our previous trainings that achieved this goal. A research assistant will complete brief tracking logs (1/workshop, 34 total) that will include the number attending the AAT workshop (*reach*). The research assistant will also complete checklists (1/clinic, 34 total) to assess *fidelity* (whether interventions were delivered as intended). We will calculate the percentage of the intervention curriculum covered as intended. To qualitatively assess *adoption* (AAT use), *appropriateness* (AAT relevance), *feasibility* (ability to facilitate AAT), and *sustainability* (ability to use AAT over time), key informant interviews will use measures and analyses described in Activity 3c.[74]

Incentives and use of AA: We will quantitatively assess all implementation outcomes in the participant surveys (see Activity 2c). For example, Dr. Weiner (Intervention Core) has validated items for *acceptability*, *adoption*, and *feasibility* that we will use with respect to the use of AA and financial incentives.[76] We will measure *fidelity* regarding the use of AA by asking providers about their use of each component (presumptive announcement, connect and counsel, and follow-up) using a single item with a 5-point Likert scale response for each component. We will survey providers regarding *reach* (e.g., did providers use AA for most patients?) and *sustainability* (do providers plan to keep using AA/incentives?). We will also probe all implementation outcomes qualitatively in the key informant interviews (described in Activity 3c).

Analysis. We hypothesize that financial incentives will be associated with favorable implementation outcomes in response to having money at stake. We will use *t*-tests to compare trial arms on quantitative implementation outcomes. We will also repeat the analyses from Activity 2c with the quantitative implementation outcome measures as the dependent variable in separate models. For qualitative data, we will use the analytic methods described in Activity 3c, using a priori codes guided by the Proctor framework.[58] We will integrate quantitative and qualitative results using a joint data display.[77]

Integration. We will share findings with Project 4 for inclusion in the web-based decision support tool.

3c. Characterize determinants of AAT and financial incentives implementation and strategies for improving HPV vaccination that providers and clinics use in response to financial incentives

Measures. We will pilot the interview guide with someone with knowledge of AAT and financial incentives to ensure the interview guide's clarity and comprehensiveness; results will not be included in final analyses. The final interview guide will explore determinants of AAT and financial incentives implementation and other strategies to improve HPV vaccination that clinics use in response to financial incentives (e.g., team huddles). Guided by the Expert Recommendations for Implementing Change (ERIC) strategies compilation, we will ask about how they decided to distribute the incentives within the clinic, why they chose that approach and whether they would make any changes.[78] Guided by the CFIR, will also assess AAT and financial incentives implementation determinants such as leadership engagement and readiness for implementation.[59]

Analysis. Qualitative research experts from CHAI core will use a coding-based thematic analytic approach that identifies main themes within and across the in-depth interviews. We will create a common codebook with coding categories derived a priori from ERIC and the CFIR. We will upload transcripts into a qualitative software management tool (i.e., ATLAS.ti) and at least two team members will independently read and deductively code each transcript. The team will iteratively meet to review the results of the coding and reconcile any discrepancies until they reach consensus. The coding team will generate summary reports of each code across interviews, assessing the degree to which the code emerged in the data. We will generate a key summary report that summarizes each code across the interviews and highlight the key themes with direct participant quotes.

3d. Contribute module to AAT Intervention Package

Project 2's contribution to the AAT Intervention Package will summarize our findings on the effectiveness of financial incentives to boost the impact and implementation of AAT. The module will present Activities 3a-b findings regarding AAT and financial incentives cost-effectiveness, acceptability, appropriateness, and other implementation outcomes to support healthcare system leaders' adoption decision. To inform quality improvement managers' implementation efforts, we will include a context assessment tool based on Activity 3c findings regarding determinants of AAT and financial incentives implementation (e.g., engaging system leadership). We will also compile best practices from the behavioral economics literature regarding incentive size, payment frequency, methods to promote cooperation between providers, and suggestions to align incentives with payment models currently in place. **The results of Aim 3 will provide crucial information on the costs for healthcare systems to facilitate the adoption and implementation of effective interventions to improve HPV vaccine communication and increase HPV vaccination uptake.**

Potential Challenges and Solutions

Covid-19. The Covid-19 pandemic has changed clinic priorities and workflows. We will work with clinics during recruitment and the trial to accommodate to this new environment as needed. For example, we have experience delivering AAT remotely/online (over 50 remote trainings so far). Importantly, the Covid-19 crisis has reduced routine vaccination,[4,5] making the need for increased HPV vaccine uptake even greater.

Generalizability. We acknowledge that our results may not generalize to clinics outside of healthcare systems or using other EHR systems. However, primary care practices are rapidly consolidating in healthcare systems and Epic is one of the most used EHR systems nationwide.

Scalability. For financial incentives to be adopted, payers or healthcare systems would need to adopt them. Many large private insurers, including Blue Cross and Blue Shield of North Carolina, are adopting pay-for-performance contracts with providers. Given this, and our preliminary evidence suggesting providers' support for it, we believe incentives for HPV vaccination can become sustainable and scaled up.

Relevance to Program Project Theme

The **IMPACT Program Project theme** is amplifying the impact of a Research-Tested Intervention Program to improve HPV vaccine communication in healthcare systems. Project 2 addresses this theme via financial incentives to motivate providers to apply what they learn in AAT. Three projects will contribute to the national survey, led by the **Data Core**, which provides each research project access to a higher-quality sample of a more diverse group of health professionals than would be possible if each project conducted a survey independently. With help from the cores, standardized implementation (**Intervention Core**) and impact (**Data Core**) information will be shared with **Project 4** for cost-effectiveness modeling and decision support tool development. The research projects will each contribute a new element to the **AAT Intervention Package**. Project 2 will contribute a module on best strategies for financial incentives for HPV vaccination. We will also work with the **Intervention Core** to disseminate our findings widely to scientific, clinical, and public health audiences through our team's website (hpvIQ.org), scientific publications, conference presentations, and stakeholder engagement. The proposed research can help reduce the incidence of HPV and HPV-associated cancers by increasing adoption of HPV vaccine communication interventions in healthcare systems.

Table 8. Research Timeline

		Year 1				Year 2				Year 3				Year 4				Year 5			
	Quarter	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Hire staff, IRB application		■																			
Aim 1	1a: Conduct national survey	■	■	■	■																
	1b: Refine feedback report			■	■	■															
Aim 2	2a: Randomize / recruit clinics						■	■			■	■									
	2b: Assess HPV vax							■	■	■	■	■	■	■	■	■	■				
	2c: Examine intrmed outcomes										■	■			■	■					
Aim 3	3a: Assess cost per initiated							■	■	■	■	■	■	■	■	■					
	3b/c: Examine implm outcomes and determinants										■	■			■	■					
	3d: Draft package module																		■	■	■
Disseminate findings						■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■

PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001

Expiration Date: 02/28/2023

Use of Human Specimens and/or Data

Does any of the proposed research in the application involve human specimens and/or data *	○ Yes ● No
Provide an explanation for any use of human specimens and/or data not considered to be human subjects research.	
Are Human Subjects Involved	● Yes ○ No
Is the Project Exempt from Federal regulations?	○ Yes ● No
Exemption Number	❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8
Other Requested Information	

Human Subject Studies

Study#	Study Title	Clinical Trial?
1	The impact of clinic-level financial incentives on HPV vaccine communication and uptake	Yes

Section 1 - Basic Information (Study 1)

OMB Number: 0925-0001

Expiration Date: 02/28/2023

1.1. Study Title *

The impact of clinic-level financial incentives on HPV vaccine communication and uptake

1.2. Is this study exempt from Federal Regulations * ○ Yes ● No

1.3. Exemption Number ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8

1.4. Clinical Trial Questionnaire *

1.4.a. Does the study involve human participants?	● Yes	○ No
1.4.b. Are the participants prospectively assigned to an intervention?	● Yes	○ No
1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?	● Yes	○ No
1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?	● Yes	○ No

1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable

Section 2 - Study Population Characteristics (Study 1)

2.1. Conditions or Focus of Study

- To examine whether financial incentives tied to clinic-level improvement in HPV vaccination rates can further improve HPV vaccine communication and uptake.

2.2. Eligibility Criteria

Aim 1Activity 1b• Electronic health record (EHR) data will be queried for patients meeting the following criteria:1) Aged 9 to 172) Had at least one visit with a pediatric or family medicine clinic within the UNC system in the prior two years• Usability testing will be conducted with 6-8 providers meeting the following criteria:1) HPV vaccine providers (physicians, physician assistants, and nurse practitioners)2) Provided HPV vaccinations to adolescent patients aged 9-17 in the prior two yearsAim 2Activity 2aClinics will be recruited into the trial that meet the following criteria:1) Specialize in pediatric or family medicine2) Have at least 50 or more patients aged 11 to 12 in the prior two years3) Have at least two HPV vaccine provider who provided HPV vaccine in the prior two years4) No Announcement Approach Training (AAT) in last 6 months or coming 6 months5) No existing financial incentives tied specifically to HPV vaccination6) HEDIS HPV up-to-date measure < 80%.Activity 2bVaccine coverage at the clinic level will be evaluated using EHR data for patients who meet the following criteria:1) Aged 11-12 or 13-172) Had at least one visit with a clinic that was recruited into the trial in Activity 2a during the studyActivity 2cChange in communication cognitions and behaviors will be evaluated based on a survey of providers who meet the following criteria:1) Providers at one of the clinics recruited into the trial in Activity 2aAim 3Activities 3b and 3c1) Providers and clinic managers from the clinics participating in the Aim 2 trial (see clinic inclusion criteria above)

2.3. Age Limits	Min Age: 18 Years	Max Age: 99 Years
2.3.a. Inclusion of Individuals Across the Lifespan	InclusionofLifespanP2r1045595414.pdf	
2.4. Inclusion of Women and Minorities	InclusionWomenMinoritiesP2r1045595415.pdf	
2.5. Recruitment and Retention Plan	RecruitmentP2r1045595416.pdf	
2.6. Recruitment Status	Not yet recruiting	
2.7. Study Timeline	TimelineP2r1045595417.pdf	
2.8. Enrollment of First Participant	12/01/2021	Anticipated

INCLUSION OF INDIVIDUALS ACROSS THE LIFESPAN – Project 2

The surveys and interventions will focus on primary care professionals, so only adults working in their professional roles in pediatric primary care will be included in the studies. The effectiveness of the planned interventions for the Aim 2 trial will be evaluated using electronic health record data to calculate the proportion of adolescent patients ages 9-17 years who have initiated the HPV vaccine series and the proportion of adolescent patients who are up to date on HPV vaccinations. We will not interact with children as part of the trial or other planned studies.

INCLUSION OF WOMEN AND MINORITIES – Project 2

The proposed research will include women and minorities throughout. Our estimates for inclusion of women and minorities appear in the targeted/planned enrollment tables. We anticipate the inclusion of women and minorities in these calculations to be representative of the distribution of women and minorities providing and receiving HPV vaccines at pediatric and family medicine clinics affiliated with NCnet, our practice-based research network partner.

RECRUITMENT AND RETENTION PLAN – Project 2

We will recruit participants for several data collection strategies to satisfy the specific aims: web-based surveys, cognitive testing, a randomized clinical trial (RCT), and qualitative phone interviews.

Aim 1 Web-based Survey and Cognitive Testing

National primary care team survey

In Aim 1, Activity 1a, we will contribute to the national primary care team survey, jointly with Projects 1 and 4 and the Data Core. Project 2 will add questions to assess providers' perceptions (e.g., acceptability, effectiveness) of HPV vaccine-related financial incentives and behavioral nudges. The Data Core will contract with WebMD Market Research to recruit 2,500 members from its standing, online panel of pediatric primary care professionals. The company will use quota-based sampling to recruit ~500 participants from each of 5 groups: pediatricians; family physicians; nurse practitioners and physician assistants; registered nurses; and medical assistants. WebMD will invite panel members to join the survey via email and targeted ads. Participants will receive up to $45 for participating. Based on the panel's prior performance, we anticipate a response rate of ≥60%.

Cognitive testing

In order to ensure readability and comprehension of the national survey measures for Project 2 and a subset of four to five demographic items, we will employ cognitive testing using "think aloud" exercises with eight local physicians from the NCnet practice-based research network. Recruitment is expected to take 2-3 weeks and interviews will be conducted on a rolling basis. We will offer each participant a $100 gift card for completing the interview. Interviews are expected to take ~30 minutes.

Aim 2 RCT

System and clinic recruitment

In Aim 2, Activity 2a, clinics will be recruited into the RCT. Dr. Hernandez will lead recruitment efforts using past NCnet relationships and proven processes. The processes include engaging system leadership first, a focus on clinic workflow, on-site visits by Drs. Hernandez and Trogdon, and adequate participation incentives. Participating clinics will receive $2000 each, $1000 upon completion of baseline data collection and $1000 upon completion of final data collection. Clinics will be recruited in two phases, half in Year 2 and half in Year 3 so that processes can be adapted in the second phase. For each participating clinic, we will identify one or two key contacts for the project with whom the research study has primary communication. Clinics in the control arm will be waitlisted to transition to the intervention, which will run for an additional 12 months after the RCT, to increase acceptance within the healthcare systems and to avoid negative reactions in the control clinics. Since the data used for the primary and secondary analyses come from electronic health records (EHRs) that are integrated within the clinics, completion and initiation rates can still be calculated for clinics who dropped out of the trial.

Pre- and post-training trial participant surveys

For each Announcement Approach Training (AAT) workshop, pre- (T0) and post-training (T1) surveys will be collected from each participant to assess provider, clinic, and patient-volume characteristics as well as changes in participant knowledge, self-efficacy, and intentions. With a total of 34 clinics recruited, we expect approximately 6 participants in each training from each clinic for a total of approximately 204 participants. Surveys will take 3-5 minutes each. The post-training survey is part of the requirement for earning continuing medical education and continuing education credit. Providers will receive $100 to complete T0 and T1 surveys.

Trial participant follow-up surveys

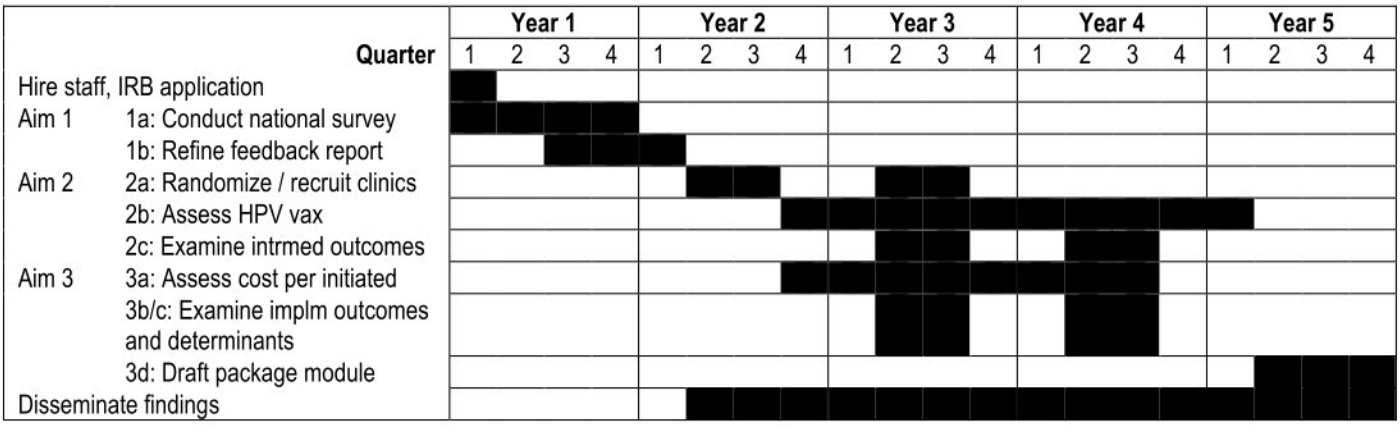
Twelve months after the AAT workshops take place in the clinics, trial participants from each clinic will complete an online follow-up survey (T2). Those who complete the follow-up online surveys will be paid $100. We will use web-based RedCap surveys for T2; to improve response rates, participants will also have the option to complete a paper form of the survey and mail it back to us. We will send up to six email and phone

reminders to improve response rates at T2. The provider survey will also be used in Activity 3c in conjunction with a phone interview (described below) to characterize strategies providers and clinics used in response to financial incentives.

Aim 3 Qualitative Phone Interview

Under Aim 3 (Activity 3c) we will recruit and interview a sample of two providers and one clinic manager from approximately nine clinics who received the intervention. The qualitative interview will be 25-30 minutes long and will be conducted by an experienced interviewer from the CHAI core over the phone. Participants will receive $100 for participating in the interview.

STUDY TIMELINE – Project 2



Aim 1

The timeline for conducting the national primary care team survey (Activity 1a), querying electronic health record (EHR) data to calculate provider-level HPV vaccine coverage and designing the feedback report (Activity 1b) requires quick and nimble implementation. Key to our ability to meet this timeline is having a research team that has worked together in the past on successful projects, having team members work parallel on tasks, and relying on the extensive previous work of our experienced investigators. For Activity 1a, WebMD's existing panel of healthcare providers allows us to quickly access large national samples. In addition, the EHR data queried in Activity 1b are collected at the time of service and can be analyzed within days of data collection over secure servers.

Aim 2

The randomized clinical trial in Aim 2 will be conducted in two waves, in Years 2 and 3, allowing for time to address unexpected challenges that may occur. HPV vaccine outcomes will be measured at 6 months, 12 months, and 18 months post randomization. Trial outcomes will be calculated using EHR data that are collected at the time of service and already integrated within the healthcare systems. We will survey all providers in participating clinics (n=~204) at baseline (immediately before the AAT workshop, T0), immediately after the AAT workshop (T1), and at the end of the intervention 12 months later (T2). Year 4 will allow for some delay in recruitment, but will largely be used to analyze data from the RCT.

Aim 3

Under Activity 3a, we will collect cost data from each AAT workshop, from study records tracking the amount of incentives paid to clinics, from interviews with clinic leaders, and from the trial participant surveys at T0 and T2. Under Activity 3c, we will recruit a sample of two providers and one clinic manager from approximately nine clinics from the intervention arm in the trial. To ensure timeliness of survey data collection, interviews will be conducted by an experienced interviewer from the CHAI core and will take place over the phone.

Dissemination

We will disseminate findings from the proposed research in Year 2-5. In Year 5, the trial team will refine the materials developed for the interventions to determine the best practices to be included in the AAT Intervention Package and disseminated to healthcare systems.

2.9. Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
Study 1, IER 1	Domestic	Family medicine and pediatric clinics

Inclusion Enrollment Report 1

1. Inclusion Enrollment Report Title* : The impact of clinic-level financial incentives on HPV vaccine communication and uptake

2. Using an Existing Dataset or Resource* : ❍ Yes ● No

3. Enrollment Location Type* : ● Domestic ❍ Foreign

4. Enrollment Country(ies): USA: UNITED STATES

5. Enrollment Location(s): Family medicine and pediatric clinics

6. Comments: Aim 1: For IER for Activity 1a, please refer to the Data Core. IER below is for Activity 1b. EHR data will be queried for adolescent patients who visit clinics participating in the Aim 2 trial. Numbers below are an estimate and we will not know actual sample sizes until the time of the study.

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	78	75	35	35	223
Asian	448	428	22	22	920
Native Hawaiian or Other Pacific Islander	15	16	21	14	66
Black or African American	3932	3732	182	175	8021
White	10876	10331	1510	1432	24149
More than One Race	615	582	398	382	1977
Total	15964	15164	2168	2060	35356

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	0	0	0	0	0	0	0	0	0	0
White	0	0	0	0	0	0	0	0	0	0
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0	0	0

Section 3 - Protection and Monitoring Plans (Study 1)

3.1. Protection of Human Subjects	ProtectionHsP2r1045595418.pdf
3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?	● Yes ○ No ○ N/A
If yes, describe the single IRB plan	MultisiteStudyP2r1045595419.pdf
3.3. Data and Safety Monitoring Plan	DsmpP2r1045595420.pdf
3.4. Will a Data and Safety Monitoring Board be appointed for this study?	● Yes ○ No
3.5. Overall structure of the study team	StudyTeamP2r1045595421.pdf

PROTECTION OF HUMAN SUBJECTS – Project 2

Risk to subjects

Human subjects involvement

The proposed project "The impact of clinic-level financial incentives on HPV vaccine communication and uptake," will take a multidisciplinary approach to identify the likely impact of financial incentives on HPV vaccine coverage and provider communication. First, we will contribute a web-based national primary care team survey to understand their current experiences with, and preferred designs for, financial incentives with behavioral nudges (e.g., prepayment contracts, peer comparison feedback). Then we will calculate provider-level HPV vaccine up-to-date and initiation rates for the family medicine and pediatric clinics participating in the Aim 2 randomized clinical trial (RCT). Rates for each participating clinic will be calculated based on EHR data for adolescent patients (ages 9-17) who have visited the respective clinics in the prior two years. To assess the impact of financial incentives on HPV vaccine uptake and provider communication, we will conduct an RCT that randomizes clinics to intervention and control arms. Trial outcomes will be calculated using EHR data of adolescent patients (ages 11-17) at the participating clinics. Secondary outcomes will be assessed via surveys of participating providers before and after the intervention. At the end of the RCT, we will interview two providers and one clinic manager at approximately nine participating clinics to characterize the strategies that were used in response to the intervention. Finally, cost data for each participating clinic will be collected through the interviews and time and expense logs completed by Announcement Approach Training (AAT) facilitators.

Source of materials

We will use several data collection strategies to achieve the goals discussed above: web-based national survey of primary care team members, cognitive testing, EHR query, surveys of RCT providers, phone interviews, and web-based cost logs.

National primary care team survey. In collaboration with the Data Core and the Projects, we will conduct a national provider survey with approximately 2,500 primary care team members involved in HPV vaccine provision. Please refer to the Data Core for Inclusion Enrollment Report and other Human Subjects information for the national survey.

Cognitive testing. In order to ensure readability and comprehension of the national survey measures for Project 2 and a subset of four to five demographic items, we will employ cognitive testing using "think aloud" exercises with eight local healthcare professionals from the NCnet practice-based research network. The cognitive testing will consist of asking participants to answer an item that will be included in the web-based survey, asking what they believe the question was trying to ask, and what they intended by their answer. We will temporarily have participants' names and contact information for the purpose of scheduling and conducting the interview and providing incentives. However, identifying information will not be linked to participants' data.

EHR query. In Aim 1 (Activity 1b), we will query EHR data of clinics participating in the RCT to calculate HPV vaccine initiation and up-to-date rates. For each clinic, rates will be calculated based on EHR data for adolescent patients aged 9-17 who visited the respective clinic at least once in the prior two years.

RCT and provider surveys. In Aim 2, we will conduct an RCT to assess the impact of financial incentives on HPV coverage and provider communication. Randomization will occur at the clinic level. EHR data for adolescent patients aged 11-17 who visited the respective clinics at least once during the study will be used to calculate trial outcomes. In Activity 2c, we will survey all providers in participating clinics (n=~204) at baseline (T0), immediately after the AAT workshop (T1) and at the end of the intervention 12 months later (T2). We will use paper surveys for T0 and T1 and web-based RedCap surveys for T2. No survey will request any identifying information or sensitive data from participants. Participants will complete a sign-in sheet that will allow us to distribute continuing medical education credits, but this sign-in sheet will not be kept with survey data.

Phone interviews. Upon completion of the trial, a phone interview will be conducted with two providers and a clinic manager at approximately nine of the clinics in the intervention arm of the trial to characterize the strategies used in response to the intervention (Activity 3c).

Web-based cost logs. AAT facilitators will complete time and expense logs that details the costs associated with each of the AAT workshops (Activity 3a).

Potential risks

We anticipate that risks to participants will be minimal and manageable. There are no biospecimens that will be collected or stored for the purpose of this proposed study. We are not specifically targeting any of the following special classes of people: prisoners, institutionalized individuals, or other special classes of subjects who may be considered vulnerable populations.

No patients will be contacted directly for the proposed study. Adolescents whose EHR data are being used in Aims 1 and 2 will not be contacted directly. Providers participating in our data collection efforts will answer questions about their professional and work beliefs and behaviors. We are not discussing highly personal or sensitive topics with any provider participants.

The main risk is breach of confidentiality. The plan for mitigating this risk is discussed below (under "Adequacy of protections against risk"). All information about human subjects will be maintained by UNC. All members of the study team will abide by applicable laws and regulations regarding the protection of patient privacy and confidentiality in human subjects research.

Adequacy of protection against risks

Recruitment and informed consent

National primary care team survey. Please refer to the Data Core for Inclusion Enrollment Report and other Human Subjects information for the national survey.

Cognitive testing. Cognitive testing will be conducted with eight local providers in NCnet. The informed consent process will occur at the beginning of the testing. The interviewer will read the consent form aloud to the participant to explain the study's purpose, potential risks, expected benefits, protection of confidentiality and time expectations. The interviewer and participant will both sign the informed consent form, and the participant will retain a copy of the form for his or her records. The consent form will include contact information for the IRB and the Principal Investigator in case participants have concerns or questions about the study.

EHR query. EHR data will be stored on a password-protected secure server and all study members who access the EHR data will be bound by a signed Data Use Agreement (DUA) to keep confidential all personal identifiers and information. The data contain information on medical procedures, diagnoses, prescriptions, and patient demographics and will be stripped of names, telephone numbers, addresses, social security numbers, medical record numbers. We anticipate the query to be exempt from the informed consent process since data are collected for administrative purposes at the time of service, no interactions with patients will take place, and direct identifiers are not available in the data.

Surveys with RCT providers. Pre- (T0) and post-training (T1) surveys will take place in the context of the AAT workshops. The UNC IRB has previously considered this activity to be quality improvement rather than human subjects research, and therefore does not require consent. If the IRB deems this activity to be human subjects research, we will use a process of passive consent used in previous trainings in which a consent form is included in the participant materials and is referred to by the facilitator. Participants are given the opportunity to ask questions about the study at that point during the training.

T2 survey participants will read an electronic version of the informed consent form before beginning the survey and will be asked to select a checkbox to confirm their consent. The consent forms for this survey will include information about the study's purpose, that there is minimal risk involved, expected benefits, that survey responses are confidential, time expectations, and that they can stop the survey or not answer any question at any time. The form will also include contact information for the IRB and Principal Investigator in case participants have concerns or questions about the study.

Phone interviews. The consent procedures for the phone interview are identical to "Cognitive testing" with the following modifications for telephone interviews. The study team member will email the consent form in advance, and at the start of the call, they will review the consent form using the process described above and ask for verbal consent to participate before proceeding. We anticipate obtaining informed consent verbally will be appropriate given that participants are adults and the interviews will not cover sensitive information. In-depth interviews will be recorded and transcribed for accuracy. Audio recordings will be destroyed once they have been transcribed and any identifying information will be redacted from the transcriptions.

Web-based cost logs. The consent procedures for the web-based cost logs are identical to "Surveys with RCT providers" above.

Protection against risk

The informed consent process will ensure that participants are aware of the potential risks of participating in the study. If we need to provide informed consent for the pre- and post-trainings surveys, the participant consent form included with the training materials will also outline potential risks of participating in the study. We will also remind participants of their right to drop out of the study at any point without consequence.

We will not share information or data provided by study participants, nor will we share data accessed in the EHRs. All information will be kept confidential, and identification numbers will be used rather than the names of study participants. Survey vendors will provide us with de-identified datasets. All study materials will be kept in a locked file accessible only to key study personnel. All computer files will be stored on a secure, password-protected server and accessed on computers that are password-protected, with IRB-approved personnel having access. Audio recordings from the cognitive testing and phone interviews will be destroyed once data analysis is complete. Staff members must complete an online IRB research ethics training course and other confidentiality certification procedures upon employment. Policies regarding the confidential nature of the data collected, processed, and stored will be explained to all personnel, who must then sign a confidentiality agreement before being allowed access to the confidential information. In addition to this initial training, we will reinforce the need for careful and confidential handling of data at staff meetings.

Potential benefits

By taking part in this study, participants may increase their knowledge of the impact of financial incentives on HPV vaccine uptake and provider communication. Participants may also experience personal satisfaction of knowing they have contributed to a research project aimed at understanding interventions that may improve the provision of the HPV vaccine. They will also receive monetary compensation for the time they invest in the study.

Importance of knowledge to be gained

Given that the risk to participants is minimal and manageable, the knowledge to be gained has the potential to fill an important research gap. Specifically, scientific findings will provide evidence for the value of HPV communication interventions. Ultimately, this work will greatly improve public health by reducing the incidence of HPV-associated cancers.

MULTI-SITE STUDY: SINGLE IRB PLAN – Project 2

The proposed study “The impact of clinic-level financial incentives on HPV vaccine communication and uptake” will implement a single IRB plan. Under Aim 1, UNC will collect data from a web-based national survey subcontracted through WebMed (Activity 1a) and electronic health records (EHRs) at trials participating in the randomized clinical trial (Activity 1b). EHR data and data collected through phone and web-based surveys will also be used to address the Aims 2 and 3. The Project Lead, Dr. Trogdon, will provide oversight of the research at all participating sites.

UNC will exercise authority and responsibility on behalf of our research partners and submit a single IRB application for review of human subjects research, in accordance with NIH policy for research protocols that are carried out at more than one site in the United States. Our research partners have agreed to rely on the proposed single IRB. The Project Lead and Project Manager will communicate directly with our research partners to ensure all study related procedures and documents are approved by UNC’s IRB. Prior to initiating the study, we will sign an authorization/reliance agreement that will clarify the roles and responsibilities of the single IRB and participating sites with our research partners. UNC will maintain records of the authorization/reliance agreements and of the communication plan.

DATA AND SAFETY MONITORING PLAN – Project 2

The Project Lead, Dr. Trogdon, will be responsible for monitoring of the data and safety of the study participants. The proposed studies will be monitored by the UNC IRB. Any unanticipated problems, serious and unexpected adverse events, deviations, or protocol changes will be promptly reported by the Project Lead to the IRB and sponsor agency, if appropriate.

UNC Lineberger Comprehensive Cancer Care Center has an established Data Safety Monitoring Plan in place. The UNC Lineberger's Director and the Associate Director for Clinical Research have the overall responsibility for policy on the data and safety monitoring of clinical trials. The Data Safety Monitoring Subcommittee (DSMS) is the primary agent for the assuring data and safety monitoring. The DSMS meets monthly and has the following responsibilities: 1) Reviewing serious adverse event reports from all active clinical trials and assuring that these have also been reported to the IRB and other appropriate agencies; 2) Reviewing data and safety monitoring reports that are required of all active clinical trials; and 3) Recommending appropriate actions (closure, increased monitoring, etc.) to the IRB based on reviews of serious adverse events and periodic reports.

The DSMS findings, when necessary, will be sent to IRB and to the School of Medicine's Data and Safety Monitoring Board (SOM-DSMB). Following a joint session that will include the SOM-DSMB and a representative of the DSMS, a final report and recommendation regarding continuation or closure of a study will be made to the IRB, reflecting input from both groups. Final responsibility and authority for closing or amending such trials will rest with the IRB.

NIH grant applications require clinical trials to have a data safety and monitoring plan, but some do not require a data safety monitoring board (DSMB) or data monitoring committee (DMC). The NCI in 2001 stated, "there is no longer a blanket requirement for DSMB (DMC) in the cases of low-risk behavioral and nutritional trials... All such trials should include a data…monitoring plan, but this may or may not include a DSMB (DMC)". We believe that our research projects are low risk and do not meet the definition of clinical trials requiring a data safety monitoring board. However, to the ensure maximum protection of human subjects, we will submit our research project information to the SOM-DSMB listed above and allow them to make the final decision regarding risk to participants and whether our studies should receive their supervision. We do not anticipate that our studies will require ongoing supervision by the SOM-DSMB.

OVERALL STRUCTURE OF THE STUDY TEAM – Project 2

The organizational structure of the study team as it pertains to IMPACT Project 2's proposal is below. In addition to the scientists listed below, our team will also have access to biostatisticians with expertise in surveys and randomized clinical trials (RCTs) through the Data Core, who will consult on key design and analysis issues. Our multidisciplinary group has the expertise in health economics, behavioral economics, pediatrics, RCTs, implementation science, and health services research required for a successful study.

UNC Study Team

- *Justin Trogdon*, PhD, will be the Project Lead for the study and will take primary responsibility for the research and administration of this award. He will meet weekly with the full study team to ensure high quality research is conducted on time, within budget, and in compliance with the ethical requirements of the IRB. Dr. Trogdon will lead dissemination including manuscript preparation and conference presentations.
- *Michelle Hernandez*, MD, a Co-Investigator, will lead recruitment of clinics for the RCT and provide mentorship and clinical guidance to the study team. She will attend regular project meetings and contribute to dissemination of study findings.
- *Sarah Birken*, PhD, will advise on the implementation science measures and evaluation in Aim 3.
- *Kathleen Mottus*, the NCnet Project Manager, will assist Dr. Hernandez and the research team with the recruitment of clinics for the trial and will support clinic relationships and communication throughout its duration. She will regularly attend meetings.
- *Project Manager*, to be named, will be responsible for managing daily project operations for the study and will serve as the liaison between the Project Lead, project team, and study contractors. The Project Manager will also coordinate research activities, such as writing research protocols, managing the project budget, submitting IRB protocols and revisions, developing data collection instruments, managing data collection, and preparing reports, conference presentations, and manuscripts to disseminate findings. Dr. Trogdon will supervise the Project Manager.
- *Graduate Research Assistants*, to be named, will help the study team with carrying out administrative and research tasks including supporting data cleaning, data analysis, and interpretation of findings. The Research Assistants will also assist the study team in developing dissemination materials such as conference posters, presentations, and manuscripts. The Project Manager and Dr. Trogdon will jointly manage the Research Assistants.
- *Brian Cass*, the programmer, will assist with data cleaning and data analysis for the electronic health records data. In addition, he will work with the Connected Health Applications and Interventions (CHAI) Core on the development of the feedback report.
- *CHAI Core* will lead refinement of the peer comparison feedback report and qualitative research. CHAI Core has extensive experience in qualitative research graphic design, including designing personalized feedback via text, email, and app notification.

External consultants

- *Harsha Thirumurthy*, PhD, a consultant, will bring expertise regarding the design of the study intervention and clinical trial processes. He will attend regular project meetings and contribute to dissemination of study findings.

Clinical Advisory Board

- We will periodically consult the Clinical Advisory Board convened by the Intervention Core. The Board includes pediatricians, nurses, medical assistants, and other supporting providers and meets quarterly. We will bring questions about the clinical context for Announcement Approach Training workshops and financial incentives.

Section 4 - Protocol Synopsis (Study 1)

4.1. Study Design

4.1.a. Detailed Description

Recruitment: Clinics will be recruited from NCnet, a practice-based research network at UNC. To be eligible to participate, clinics must meet the following inclusion criteria: 1) specialize in pediatric or family medicine, 2) have 50 or more patients aged 11 and 12 years in the previous two years, and 3) have at least 2 HPV vaccine provider who provided HPV vaccine in the previous two years. Clinics will be ineligible for the RCT if they had taken part in Announcement Approach Training (AAT) in the previous six months or planned to do so over the next six months, already have financial incentives specifically for HPV vaccination, or are already meeting the goal of 80% up-to-date on the HEDIS measure. Randomization: After recruitment, clinics will be randomly assigned to one of two arms. Clinics in the first arm will receive AAT (control). Clinics in the second arm will receive the same AAT and a financial incentive via commitment contract tied to clinic-level improvement in HPV vaccine coverage (intervention). Clinics in the control arm will be wait listed to transition to receive the intervention after the end of the RCT to increase acceptance within healthcare systems and to avoid negative reactions in the control clinics. Clinics will be blinded to their assigned arm at recruitment. Randomization will be conducted by a biostatistician in the Data Core not affiliated with this trial. Clinics will be assigned in a 1:1 proportion to the arms, stratified by the rurality of patients served and baseline HPV vaccination coverage rates to ensure balance in these dimensions across arms. Detailed description of intervention: Announcement Approach training (AAT)Clinics in both arms will receive AAT. The AAT instructs providers to use a presumptive recommendation, in which the provider announces the vaccines the child is due for, assuming the family is ready to vaccinate. AAT is one hour, conducted in clinic and provides continuing medical education credit for attendees. Financial Incentives Clinics in the intervention arm will be eligible to receive clinic-level financial incentives if they meet pre-determined targets for HPV vaccination coverage. We propose three sizes of incentives for each tiered goal met by the clinic. The clinic-level incentives will be scaled to equal $1000 per provider, but aggregated and paid to clinic, for reaching highest tier, an absolute goal of 80% of patients meeting the HEDIS up-to-date measure. To keep incentives salient for clinics well below 80%, we will provide smaller bonuses for improvements relative to baseline. These levels were supported as salient by interviews with providers and clinic managers in the pilot phase. Finally, providers in the intervention arm will receive monthly, automated provider feedback of each providers' HPV vaccination rates relative to other providers in the clinic.

4.1.b. Primary Purpose: Prevention

4.1.c. Interventions

Type	Name	Description
Other	AAT and clinic-level financial incentives (intervention)	The Announcement Approach Training (AAT) instructs providers to use a presumptive recommendation, in which the provider announces the vaccines the child is due for, assuming the family is ready to vaccinate. AAT is one hour, conducted in clinic and provides continuing medical education credit for attendees. Providers in the intervention arm will also receive monthly, automated provider feedback of each providers' HPV coverage relative to other providers in the clinic. Clinics in the intervention arm will also be eligible to receive clinic-level financial incentives if they meet pre-determined targets for HPV vaccination coverage. The clinic-level incentives will be scaled to equal $1000 per provider, but aggregated and paid to clinic, for reaching highest tier, an absolute goal of 80% of patients meeting the HEDIS up-to-date measure. To keep incentives salient for clinics well below 80%, we will provide smaller bonuses for improvements relative to baseline.
Other	AAT (control)	The Announcement Approach Training (AAT) instructs providers to use a presumptive recommendation, in which the provider announces the vaccines the child is due for, assuming the family is ready to vaccinate. AAT is one hour, conducted in clinic and provides continuing medical education credit for attendees.

4.1.d. Study Phase: N/A

Is this an NIH-defined Phase III Clinical Trial? ○ Yes ● No

4.1.e. Intervention Model: Parallel

4.1.f. Masking: ○ Yes ● No

❑ Participant ❑ Care Provider ❑ Investigator ❑ Outcomes Assessor

4.1.g. Allocation: Randomized

4.2. Outcome Measures

Type	Name	Time Frame	Brief Description
Primary	HPV completion rate (HEDIS)	0 months (baseline), 6 months (preliminary), 12 months (post-intervention), and 18 months (long-run)	The primary outcome measure will be HPV vaccine completion rate as defined by current HEDIS measures (i.e., among adolescents who turned 13 in the prior 12 months) assessed at the provider and clinic levels.
Secondary	HPV vaccine initiation rate (11-12 year old patients)	0 months (baseline), 6 months (preliminary), 12 months (post-intervention), and 18 months (long-run)	Proportion of patients who turned 11 and 12 in the prior 12 months who received at least one dose of HPV vaccine at the provider and clinic levels.
Secondary	HPV vaccine initiation rate (13-17 year old patients)	0 months (baseline), 6 months (preliminary), 12 months (post-intervention), and 18 months (long-run)	Proportion of patients who turned 13 to 17 in the prior 12 months who received at least one dose of HPV vaccine at the provider and clinic levels.
Other	Use of presumptive announcements	0 months (baseline) and 12 months (post-intervention)	Provider survey: When I first talk about HPV vaccine, I use language that assumes parents are ready to vaccinate.
Other	Attitudes	0 months (baseline), immediately following AAT, 12 months (post-intervention)	Provider survey: It is important to me that my patients get a recommendation for HPV vaccine before age 13.
Other	Social norms	0 months (baseline), immediately following AAT, 12 months (post-intervention)	Provider survey: It is the norm for our team to routinely recommend HPV vaccine for patients before age 13.
Other	Perceived behavioral control	0 months (baseline), immediately following AAT, 12 months (post-intervention)	Provider survey: I feel confident our team can recommend HPV vaccine effectively for our adolescent patients.
Other	Intention to recommend	0 months (baseline), immediately following AAT, 12 months (post-intervention)	Provider survey: I intend to make sure all patients get an HPV vaccine recommendation before they turn 13.
Other	Acceptability	0 months (baseline), immediately following AAT, 12 months (post-intervention)	Provider survey: satisfaction with the intervention
Other	Adoption	0 months (baseline) and 12 months (post-intervention)	Provider survey: use of the announcement approach
Other	Appropriateness	0 months (baseline), immediately following AAT, 12 months (post-intervention)	Provider survey: relevance of AAT and financial incentives in provider's clinic
Other	Cost	12 months (post-intervention)	The cost per clinic to deliver and use interventions
Other	Feasibility	0 months (baseline), immediately following AAT, 12 months (post-intervention)	Provider survey: ability to facilitate AAT and use AA and financial incentives

Other	Reach	0 months (baseline), immediately following AAT, 12 months (post-intervention)	Attendance logs: number of providers attended AAT. Provider survey: use of announcement approach for most patients
Other	Sustainability	12 months (post-intervention)	Provider survey: plan to keep using AA/incentives
Other	Fidelity	immediately following AAT and 12 months (post-intervention)	Provider survey: whether interventions were delivered as intended and providers used all components of announcement approach
Secondary	HPV vaccine completion rate (11-12 year old patients)	0 months (baseline), 6 months (preliminary), 12 months (post-intervention), and 18 months (long-run)	Proportion of patients who turned 11 and 12 in the prior 12 months who received at two doses of HPV vaccine at the provider and clinic levels.
Secondary	HPV vaccine completion rate (13-17 year old patients)	0 months (baseline), 6 months (preliminary), 12 months (post-intervention), and 18 months (long-run)	Proportion of patients who turned 13 to 17 in the prior 12 months who received at two or three doses of HPV vaccine at the provider and clinic levels.

4.3. Statistical Design and Power — StatDesignPowerP2r1045595422.pdf

4.4. Subject Participation Duration — 12 months

4.5. Will the study use an FDA-regulated intervention? — ❍ Yes ● No

4.5.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/ Investigational Device Exemption (IDE) status

4.6. Is this an applicable clinical trial under FDAAA? — ❍ Yes ● No

4.7. Dissemination Plan — DissemPlanP2r1045595423.pdf

STATISTICAL DESIGN AND POWER – Project 2

Sample size and power

Aim 1, Activity 1a. National survey

We used a general approach to estimate the minimum sample size required to detect moderately small effects. Specifically, we estimated the sample size required to detect a 10% change in endorsement of a low-prevalence outcome between two groups of unequal size (i.e. 10% endorsement in group 1, containing 75% of the sample, and 20% endorsement in group 2, containing 25% of the sample). With an alpha of .05 and two-tailed tests, an effective sample size of 500 per healthcare professional type (e.g., physicians, nurse practitioners), for a total of 2,500 respondents, is required to obtain 80% power.

Aim 2, Activity 2b. Assess HPV vaccination uptake

Assuming 17 clinics in each arm, 112 13-year old patients per clinic not up-to-date on average, a 15 percentage point increase in the control arm (secular trend + AAT), and a intraclass correlation of 0.033 (author calculations from AAT studies), we will have 80% power to detect a minimum of an 8 percentage point difference in our primary outcome in two-sided tests at a 95% confidence level. This effect size is similar to that found in earlier studies of provider incentives for other vaccinations, some of which detected effect sizes up to 19 percentage points. We tested power varying several of our input assumptions (e.g., patients per clinic, secular trend, ICC). Our results were most sensitive to assumptions about ICC. For example, with an ICC=0.04, we would be powered to detect an effect size of 9 percentage points.

Analytic Plan

Aim 1, Activity 1a. National survey

We will describe the types of primary care team members (e.g., physicians, nurse practitioners) likely to have experience with financial incentives and behavioral nudges. We will estimate separate regression models with items for the research questions as the dependent variables. As clinics that primarily serve patients who live in rural areas are different from non-rural clinics in many dimensions that could affect their ability to respond to the incentives (e.g., lower electronic health record [EHR] adoption rates, patient mix), the explanatory variables will include provider demographics collected in the national survey (e.g., rurality of clinic). Regression models will use appropriate functional forms for each item scale (e.g., logit for 0/1 outcomes).

Aim 2, Activity 2b. Assess HPV vaccination uptake

Inferential analyses. We will consult with our biostatistician on implementation of planned analyses. The main analysis will be intent-to-treat, retaining outcomes for clinics that disenroll from the trial for any reason during the intervention. We will estimate a generalized estimating equation (GEE) model for HPV vaccination using patient-level data from the EHR (0=not up to date, 1=up to date). Using a sample of patients not yet up-to-date at baseline who visited the clinic during the study period, the GEE model will account for patients clustered by clinic. We will use a binomial link and logit family. The main effect will be an indicator for intervention arm (at the clinic level). The coefficient represents the difference in the log odds of HPV vaccination at follow-up across the intervention and control arms. We will also adjust for the following baseline covariates: sex mix of patients, mix of patients residing in rural and non-rural areas, rural/non-rural location of the clinic, total number of patients ages 11-12 and 13-17, payer mix, number of providers, history of HPV quality improvement activities, ownership structure, and patient-centered medical home status. This analysis will provide an estimate of the effect of financial incentives on HPV vaccination rates. The secondary objectives of the Aim 2 analysis will be to test the comparative effectiveness of our intervention for other outcomes. We will repeat these analyses separately for each time point (6-, 12-, and 18-month follow up) and HPV vaccine outcome (HPV initiation ages 11-12 and 13-17 and HPV completion ages 11-12 and 13-17). When initiation is the dependent variable, the sample will include patient not yet vaccinated who visited the clinic during the study period.

Exploratory analyses. Several clinic characteristics could moderate the effect of the intervention. First, clinics that primarily serve patients who live in rural areas are different from clinics that primarily serve patients who live in urban areas in many dimensions that could affect their ability to respond to information provided in the feedback and the financial incentives. *Project 4 will provide valuable information from their first aim in the*

development phase of our project about key differences in rural and urban clinics with respect to HPV vaccination. Second, clinics with higher baseline HPV vaccination rates have less room to improve. Conversely, clinics with higher baseline rates (but not yet at target) may have higher capability to implement quality improvement initiatives. Finally, the interventions can differ in their impact based on the number of providers in the clinic. Providers in smaller clinics may find it easier to cooperate, harder to "free ride" on others, and to share information and tactics. To test for moderating effects of the interventions, we will repeat the GEE models described above adding interactions of the intervention arm variable with each of the following clinic-level variables: urban/rural mix of patients, baseline HPV rates, number of providers, and sex as a biological variable.

Aim 2, Activity 2c. Examine change in provider cognitions and behavior

We hypothesize that the addition of financial incentives to AAT will improve cognitions and behavior relative to AAT alone. The proposed mechanism is that financial incentives improve *cognitions* through changing attitudes, establishing new social norms, and increasing intentions to recommend, which will change HPV vaccine recommendation *behavior*. We will estimate two-level (provider and clinic) generalized linear mixed-level regression models with a log link and Poisson family. The main effects will be an indicator for time (pre vs post), an indicator for intervention arm (at the clinic level) and an interaction of time and intervention arm. Models will include random effects for clinics and will adjust for baseline covariates listed above.

Aim 3, Activity 3a. Assess cost per additional adolescent initiating the HPV vaccine

We will calculate mean, median, and standard deviation for cost per arm per clinic and separately for fixed and variable cost per arm per clinic. We will use t-tests to compare mean costs per clinic between intervention arms. We will then calculate the difference in mean costs between intervention arms and divide by the difference in adolescents ages 11-12 initiating the HPV vaccine to estimate cost per additional initiated due to the intervention. In secondary analyses, we will examine potential economies of scale by plotting average cost per clinic against clinic size. The cost data will be shared with Project 4 using standardized tables developed by the Intervention Core and utilized by Projects 1-3.

Aim 3, Activity 3b. Examine other implementation outcomes

This analysis will compare trial arms on implementation outcomes. We hypothesize that financial incentives will be associated with favorable implementation outcomes in response to having money at stake. We will use t-tests to compare trial arms on quantitative implementation outcomes. We will also repeat the analyses from Activity 2c with the quantitative implementation outcome measures as the dependent variable in separate models. For qualitative data, we will use the analytic methods described in Activity 3c, using a priori codes guided by the Proctor framework. We will integrate quantitative and qualitative results using a joint data display.

Aim 3, Activity 3c. Characterize determinants of AAT and financial incentives implementation and strategies for improving HPV vaccination that providers and clinics use in response to financial incentives

Qualitative research experts from CHAI core will use a coding-based thematic analytic approach that identifies main themes within and across the in-depth interviews. We will create a common codebook with coding categories derived a priori from Expert Recommendations for Implementing Change and the Consolidated Framework for Implementation Research. We will upload transcripts into a qualitative software management tool (i.e., ATLAS.ti) and at least two team members will independently read and deductively code each transcript. The team will iteratively meet to review the results of the coding and reconcile any discrepancies until they reach consensus. The coding team will generate summary reports of each code across interviews, assessing the degree to which the code emerged in the data. We will generate a key summary report that summarizes each code across the interviews and highlight the key themes with direct participant quotes.

DISSEMINATION PLAN – Project 2

A key dissemination activity for Project 2 will be to create an intervention module for the AAT Intervention Package for healthcare systems. The module will describe best strategies for financial incentives for HPV vaccination to a package of interventions. The Intervention Core and Administrative Core will lead efforts to disseminate the Package.

For Aims 1-3, we will publish our findings in peer-reviewed journals, submit docket responses, and present at meetings and national conferences, such as AcademyHealth Annual Research Meeting, American Society of Health Economists, and International Health Economics Association World Congress. As appropriate, we will update materials on hpvIQ.org for others to use. We will produce press releases and other communications to document and share our research findings with the scientific community as well as other key stakeholders and advocates. Dissemination of scientific findings will help advance HPV vaccine provision efforts and reduce the incidence of HPV-associated cancers.

Specific to the Aim 2 RCT, we will register the trial with ClinicalTrials.gov prior to enrollment of the first study participant, and we will submit results and other required information to ClinicalTrials.gov within one year of the conclusion of the study. We will include text in the informed consent information for this study that states that the results of the trial will be available on ClinicalTrials.gov. We will follow the UNC Gillings School of Global Public Health procedures for ensuring the clinical trials registration and results reporting are done in compliance with policy requirements.

Delayed Onset Studies

Delayed Onset Study#	Study Title	Anticipated Clinical Trial?	Justification
The form does not have any delayed onset studies			

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