This NIDA funded Center for Prevention Implementation Methodology for Drug Abuse and HIV (Ce-PIM) is the only NIH center that is solely focused on implementation methodology. It was one of the first to focus on implementation and was instrumental in bringing the field of implementation science directly into the science of HIV. All five of its “qualifying grants,” which were a requirement of the P30, were focused on HIV research, including its interaction with substance misuse.

**Quantity of Ce-PIM Products.** Ce-PIM was successfully recompeted for a second 5 years starting September 2016. A no-cost extension year of this grant ended June 2022. During this period of funding, we have produced 144 publications, supported all 5 “qualifying grants” in successfully extending their NIH funding, have supported 37 early investigators, either directly through Ce-PIM funding or mentoring by Ce-PIM faculty. Since this cycle of Ce-PIM funding began, this center’s investigators, conducted 97 scientific presentations, and as our core dissemination strategy hosted 179 Virtual grand round presentations to the Prevention Science and Methodology Group (PSMG), which now has over 1400 Members with these presentations seen across 59 countries.

**Ce-PIM Was Instrumental in Filling a Compelling Need for Integrating Implementation Science in the HIV Field.** At the time we received funding for Ce-PIM, the Office of AIDS Research had clearly recognized the need for implementation studies, stating in their 2017 priorities for funding “the implementation of strategies to improve HIV testing, and entry, and maintenance in prevention care and services.” Indeed our application documented that there was very limited implementation science in the HIV field. We conducted a review of biomedical intervention trials for HIV testing, PrEP, or ART involving efficacy, effectiveness and/or implementation questions and found only 5 percent of 107 studies that addressed implementation. While limited elements of implementation science were present in a few Centers for AIDS Research (CFAR), we presented one of the first trainings on implementation science to the Northwestern/University of Chicago CFAR and the Columbia AIDS Research Center. We began conducting yearly reading courses in Implementation Science for both early career and more senior investigators. One outcome of this training was the generation of a pool of researchers who had sufficient knowledge and breadth to conduct reliable and valid systematic, scoping, and mapping reviews, as in the HIV and drug use fields there was limited standardization of implementation science terms as well as knowledge of frameworks and models. We assembled a team from those attending the reading course to conduct the first mapping review of implementation research in the HIV field. The gaps identified by this mapping review led to multiple presentations to introduce implementation science more formally, including to the NIH CFAR Social and Behavioral Science Research Network, the OAR, the NIH HEAL Initiative, the National Academies of Science, Engineering and Medicine, the Centers for Disease Control and Prevention, and the SAMHSA HIV Prevention Program. A major integration of implementation science into the HIV field occurred with the support of the Implementation Science Coordination Initiative (ISCI). Beginning with a meeting at Northwestern, ISCI introduced implementation science concepts and provided a shared experience for 65 NIH supplements to construct their own Implementation Research Logic Model (IRLM) \(^1\) one of Ce-PIMs new tools. ISCI has been funded now for 4 years and supported over 200 NIH funded projects focused on HIV implementation science, and has been a major force in standardizing approaches in this rapidly growing field (e.g., their HIV implementation science outcomes crosswalk and Implementation Research Logic Model are included in a number of federal FOAs and used in hundreds of research projects).

We have published a substantial number of papers involving the implementation of PrEP and ART within diverse communities.\(^2\) \(^1\) \(^7\) \(^4\) \(^5\) \(^8\) \(^9\) \(^13\) \(^15\) \(^17\) \(^49\)
Dissemination of Implementation Science to the Broader Community (B.4-Training). Our Prevention Science and Methodology Group virtual grand rounds, which have included as presenters many of the leading researchers in implementation science as well as HIV and drug misuse, have been viewed 3,000 times across 59 countries in this last year. These extensive viewings, plus the large number of publications and scientific presentations we have had, have contributed to the growth of implementation science, improvements in methodology, and its integration into implementation practice. Today, there is a much greater investment in this more direct stage of implementation science that can directly impact people’s health. According to NIH Reporter, there are approximately 400 currently funded NIH research studies where implementation science is integrated into HIV research. With our focus on methodology, our methods are now being used is widely diverse health fields, including addiction and substance misuse, mental health, cardiovascular, obesity, and other disorders, and in settings as diverse as primary care, mental health services, rehabilitation, and schools. In all of these areas our Ce-PIM faculty has had direct involvement.

Methodologic Developments in Implementation Science. We view methodology for implementation science as being comprised of four fundamental areas: measurement, modeling, design/testing/evaluation, and frameworks. Starting with frameworks, it was common at the beginning of our funding to hear that “Implementation Science is not a science,” a quote from a previous NIH institute director. There was little consideration that implementation science was a last step in the Traditional Translational Pipeline, which began with pre-intervention studies, followed by efficacy studies – these test whether an intervention could work in ideal conditions – to effectiveness studies – these test whether an intervention does work in realistic conditions, delivered through agencies with support by researchers – and finally implementation research – which tests whether an intervention can be made to work as it is institutionalized. This last step involves much engineering as science. A systems science and engineering perspective needs to be integrated with relevant implementation data – something we have termed a social systems informatics perspective. The simplest way to see the necessity of such systems thinking is to note that “best medication is worthless without a successful delivery system” that includes a syringe, transportation system, and a successful communication system that is trusted by those who could benefit. The continuing racial and ethnic disparities in PrEP and ART for HIV have analogies in COVID-19 and other vaccinations.

A second framework we have contributed to is the Health Equity Implementation Framework (HEIF), developed originally by Woodward and colleagues. While implementation research is infrequently directed towards minority populations, there are different strategies for using all available data that we have proposed. The first paradigm involves making efficient use of existing data by applying epidemiologic and simulation modeling to understand what drives disparities and how they can be overcome. The second paradigm involves designing new research studies that include, but do not focus exclusively on, populations experiencing disparities in health domains such as cardiovascular disease and co-occurring mental health conditions. The third paradigm involves implementation research that focuses exclusively on populations who have experienced high levels of disparities. The implementation research methods discussed here hold promise for overcoming barriers and achieving health equity. Ce-PIM has taken that stance that implementation science would be a complete failure if it doesn’t produce equity. Thus we are forced to consider factors that address primary causes for disparities to occur. We have recently published a new framework on “re-envisioning, retooling, rebuilding prevention science methods to address structural racism and promote health equity.” This includes a concept that it is not sufficient to measure race, but there is a need to study racism and its determinants. It needs to focus on new methods for examining the mechanisms by which such factors continue to perpetuate inequities and what implementation strategies can reverse these effects.

Regarding a third framework, we have distinguished the existing term “scaling up” from a new term called “scaling out.” The former term is appropriate when an intervention and its delivery system, which has achieve an acceptable level of evidence, is delivered to similar settings and similar populations and contexts. The latter term differentiates whether the new sites that are examined in implementation studies are delivered to different populations or through different support systems, or both. We noted that the expansion of our evidence-base to include new populations that initially were not tested-- often minorities are underrepresented in such studies – needs to transcend a much shorter pathway from efficacy to effectiveness and ultimately implementation that that pathway used to establish such evidence. For if the evidence required to re-establish evidence in a new population or through a new service delivery system takes as long as it originally did, we will never be able to
deliver on the promises of implementation science. A core approach involves mediation modeling for implementation, an approach discussed later.

In terms of measurement in implementation, we have built on the use of diverse qualitative, quantitative, and mixed measurement approaches. One fundamental issue we have addressed involves whether adaptations to standard implementation instruments still retain the same psychometric properties. Like others, we have encountered the necessity to re-word questions on standard instruments, such as the Evidence-Based Practice Scale, which was designed for clinicians but then applied in diverse setting where evidence meant different things and “intervention agents” included others than clinicians. Without changing the wording, as is routine in efficacy and effectiveness studies, the questions are without consistent meaning in different contexts. With such changes in wording and when delivered to different stakeholders, we found the psychometric properties to be unchanged.79

A new measurement that we have developed is the Sustainment Measurement System (SMS). Built first on (qualitative) interviews followed by (quantitative) surveys, SMS is one of the few instruments that assesses sustainability, the least studied area of implementation science87-90.

Unique opportunities to incorporate multiple measures into implementation strategies are now available. While implementation science generally has taken pains to separate implementation outcomes, such as acceptability and Reach, from individual level outcomes, there are advantages to combining such measures. For example, by combining appropriate components of Reach with evidence of individual level change in risk of HIV infection, we can assess population level impact of different implementation strategies, as we are now doing in the NIH funded Keep it Up! Trial that pits two delivery systems against one another19.

The most common concern among community and institutional partners around measuring implementation is that they are too burdensome to use. To this end, we have introduced new computational linguistics tools to collect such data as unobtrusively as possible.51,56,91-93

Another issue involving new measures is that they can create new ethical concerns. New phylogenetic data has the capacity to identify which individuals transmitted HIV to others as partners are notified, potentially causing stigma and marginalization of groups, as well as criminal charges, as transmission is still illegal in many states. Other measures can be hugely informative of developing implementation strategies to address unique needs and opportunities from a public health perspective, as the creation of recent dashboards for HIV has shown.

We now turn to methodologic advances in design that we have made. Throughout these last 5 years, we have developed a variety of new designs and applied them to test implementation strategies or bundles in diverse settings. Some of these designs are based on non-randomized studies, while many are now using randomization in different ways than more traditional individually-based randomized clinical trials or group-based randomized trials. In particular, we have emphasized the use of what we call roll-out trials, where individual sites (e.g., clinics) are randomized to when they begin different phases of implementation. Such designs are extensions of the standard stepped-wedge trial, which only has a single set of steps and two wedges. These designs have strong statistical power, as they provide both within-site comparisons, as each site transitions to a new implementation strategy, as well as between-site comparisons, as at each time period one can compare implementation outcomes for those sites in at least two different implementation conditions. Furthermore, community and institutional organizations generally feel comfortable participating in such randomized roll-out designs for two reasons. First, because implementation studies rely on an intervention (or combined intervention) that has already been shown to be effective in some setting, no site in a roll-out trial is resigned to stay in a control condition the way traditional randomized trials are conducted. Indeed, as implementation science experiments that introduce a new intervention, or de-implement one that is not effective, no longer retain any justification for equipoise, withholding such evidence-based conditions would be unethical. Second, the fair way that timing is randomly assigned to settings can benefit both those that go early – as they have early access to an intervention that is likely to be beneficial, as well as those who go later, as they may benefit from improvements in implementation throughout the trial. Indeed, we have proposed the testing of criterion-based implementation hypotheses that precisely test whether Reach is improved across the trial.
Recently, there has been a push-back against the use of classic stepped-wedge trials design, and there is a sense among some at the National Institutes of Health that their promise should be tempered if not discarded for other designs such as a parallel group randomized trial. We recognize that the classic stepped-wedge trial does partially confound the new intervention/implementation with time, because all sites cross over to this new condition, thus occurring on average later that the earlier condition. However, we have noted in several publications that other variations of roll-out design are either fully protected against this partial confounding (say for example a head-to-head implementation trial testing two implementation strategies against one another as they deliver the same intervention) or can adjust for time in different ways. We have recently proposed a hybrid type II randomized roll-out trial to test a suicide prevention program in the US Air Force that accounts for time trends in suicide attempts by including a large number of bases that are not subject to the randomized roll-out. We anticipate that more sophisticated roll-out trials will be used to carry out hybrid type II, type III, and pure implementation trials.

There is now a preponderance of hybrid type II designs, which purport to address both effectiveness and implementation questions. While hybrid type II designs can be very efficient, relatively few of these designs are conducted with sufficient statistical power to address both effectiveness and implementation. We have designed a hybrid type II trial that has sufficient statistical power to address both types of hypotheses, in an ongoing trial to reduce suicide risk behavior in Hispanic adolescents using an eHealth preventive intervention delivered through primary care57, a follow-up hybrid trial of a Familias Unidas trial that is just being completed58. The complexities of fitting in both effectiveness and implementation components with sufficient sample sizes was solved without sacrificing power on each of these two components.

A different design consideration that we have developed is the use of adaptive implementation strategies in delivering the same underlying evidence-based intervention to accommodate sites that need additional facilitation expertise. This design begins with a standardized didactic presentation in which we expect a few sites to succeed in achieving target implementation goals. For those sites that do not reach their goals under this inexpensive presentation and toolkit, we introduce a randomized trial that tests whether external or internal facilitation provides better outcomes. We have developed and received funding, led by Mark McGovern at Stanford, for such adaptations in strategies in delivering opioid treatment programs within sites that have not previously used them. We also anticipate that such adaptive implementation strategies will have use in diverse health fields.

Regarding statistical analysis and power in implementation trials, we have conducted a large number of simulations of implementation designs where sites are first randomized, then clustered together afterwards in learning collaboratives or networks. Because of clustering after assignment, one can no longer consider the outcomes of sites in the same learning collaborate as independent of one another. Mixed effects models are needed to account for such clustering. We have clearly identified ways to fit such effects in learning collaborative trials, and shown that routine analyses that either ignore such clustering after randomization or borrow models for parallel group randomized trials lead to incorrect analyses54.

Turning to modeling, a large portion of our work in this area has relied on agent-based models (ABMs). These ABMs are extremely valuable in modeling complex system behavior, such as those that underlie implementation strategies. For us, such modeling of complexities is a missing component in translating evidence-based interventions to successful implementation within specific contexts. For example, PrEP was initially shown to have efficacy and effectiveness among adult men who have sex with men (MSM), but this was not initially tested among MSM youth, nor with substantial numbers of minority MSM who are high risk for HIV infection. We will never have the time or funding to evaluate a good range of implementation strategies that seem to have prima facia evidence of ways to deliver PrEP in these larger populations at risk. In its place we have proposed the use of simulations involving ABMs, in what we call Model-Driven Decision Making. Model-driven decision making is an extension of the epidemiologically based data-driven decision making, which only go part way in helping decision makers make use of data. Model-driven decision making has two general components to inform implementation choices. First, it involves building a lasting partnership between modelers, community leaders and decision makers to clarify their values (e.g., what types of harm reduction approaches have community support), resources, and priorities. Next, through this partnership, questions are identified (e.g., how much effort
should be allocated to HIV prevention and HIV treatment), relevant local data are identified, and ABM simulations are conducted. Results of these simulations are then summarized to identify which implementation strategies are expected to have small effects and which are optimal in having impact and costing less. 

Simulation modeling is quite different from statistical modeling, as there are many more options and ABM packages producing different results compared to standards in statistical analysis that have evolved over the last 150 years. We have provided details on how to conduct replication studies using ABMs and check whether the findings are reliable (in our example using different definitions of CDC’s objective of identifying who is appropriate to take PrEP they do an excellent job of replication). A second important issue with ABMs is to clarify exactly what they do and how robust their findings are; these are critical scientific elements of our work to create an open science for high-fidelity ABMs.

A recent example of this modeling approach is our partnering with the Chicago Department of Public Health around their plan to End the HIV Epidemic, operationalized as reducing the number of new HIV infections by 90% by 2030. Simulations clearly differentiated widely different impact on 15 years’ incidence rates by different components of prevention and treatment.

We also have addressed the use of advanced statistical modeling to analyze implementation trials, hybrid trials, and summarize information needed as input for simulation studies. For example, we have summarized the immediate consequences of the COVID-19 pandemic, as well as longer-term consequences.

A major addition to implementation science is the development of the Implementation Research Logic Model (IRLM). This is a valuable implementation process itself that transcends the typical boundaries of implementation measurement, modeling, and frameworks. It forms an implementation model that links determinants (barriers and facilitators) to selected implementation strategies, their mechanism of action, and outcomes for implementation, service system change, and individual target health related outcomes.

We have just published a major paper on reimagining how prevention research can address the enduring effects of systemic racism on the health of minorities. In prevention, as well as other fields, there has been a hyper-focus on individualist biomedical explanations and solutions that can crowd out a fuller investigation of the interaction between the individual and the environment that is fundamental to racial health disparities. We call for an increased emphasis on a direct link between implementation science and health equity, a concentration on upstream and tailored interventions, overcoming the current scientific inequities of implementation studies involving minorities and minority communities, and expanding the influence of community voices, and new designs and analyses that address the forces of systemic racism.

Another point in this paper is the need to build on the strengths of minority communities, rather than attempting to overcome deficits. An example that illustrates how our implementation modeling can inform decision making involves ways to decrease the disparity in COVID-19 vaccinations and higher mortality that are borne by African Americans. While African Americans are more likely than whites to have service and essential jobs that place them at higher risk for infection, they also have more common attributes that could be integrated into ways of delivering vaccines that play to their strengths. In particular, African Americans are more likely to live in multigenerational households than whites. Often, African American mothers have a powerful voice in these families and can influence both those in their parents’ generation, as well as their own children to get vaccinated to protect all family members. If delivery of vaccinations were focused on these multigenerational families, rather than focusing on individual-level messages to get vaccinated, one would expect higher vaccinations among African Americans. Preliminary agent-based models suggest this would indeed happen.

**Ce-PIM Supplements.** We received three supplements this cycle.

**Application of implementation Science to Improve the Delivery of HIV interventions in Criminal Justice-involved (CJI) Black Men who have Sex with Men (MSM).** Brewer received a diversity supplement to address the specific needs of young African American and Latino men who have sex with men and transgender women, including those who have criminal justice involvement. In Ce-PIM’s role of serving as a national resource center for implementation science and novel approaches to wide-scale implementation of effective biomedical and other interventions related to HIV and drug abuse, we have provided resources to support...
Brewer’s work and career development. We are pleased to note that Brewer has successfully obtained a new NIH R21 (5R21MH121187) that he directs.

**Innovations in Prevention Methodology.** We obtained supplemental support from NIH’s Office of Disease Prevention (ODP) for improving the scientific rigor underlying prevention trials. A fundamental issue involves the continued incorrect analysis of preventive trials where the intervention is delivered in group or network contexts. Specifically, when there is individual level randomization followed by group-delivered interventions, one must take into account this context after assignment in the analysis. Similarly, when implementation trials are conducted where sites (e.g., clinics, counties) are assigned randomly and then combined together in learning collaboratives, this also produces non-independence across sites. In a recent paper, we have identified large classes of such trials where context after assignment needs to be addressed; we have conducted detailed evaluations of statistical methods that correctly analyze trials where one arm is delivered in a group setting and the other individually (individual randomized group delivered trials); we showed how even small intraclass correlations have a profound effect on type I error rates; we also provided detailed coding in 5 different statistical packages on how to analyze such trials appropriately. In this paper we have also proposed ways to enhance the effects of prevention programs using a multiplicative implementation strategy, an active approach that extends the current, limited view espoused by examining “spillover effects.”

**Examining how the COVID-19 Pandemic Has Affected Overdose Deaths.** We received this supplement to examine how policies and practices related to the pandemic have affected overdose deaths in Pinellas County, FL. We developed a new partnership with the county government and major service systems that deliver Medications for Opioid Use Disorder (MOUD) and HIV testing in Pinellas County FL. This county is identified on the CDC list of the top 75 counties in Ending the HIV Epidemic and also experienced a continued increase in overdose deaths in the last 3 years. Through our collaboration with the Pinellas County Opioid Task Force, we have conducted interviews of key stakeholders regarding detailed examination of the toxicology findings from 2019 through 2021. These rapid changes in delivery of medicated assisted treatment included transformation to telemedicine, take-home methadone, and increases in buprenorphine use. These interviews also identified serious challenges in implementation and sustainment, including retraining staff and patients, accessing privacy and remote services, and protecting patients from COVID infections. We also presented approaches to address infection control in opioid treatment programs. Further, we identified large disparities in opioid treatments that deeply affect African Americans in Florida’s Medicaid services.

We have also examined precisely how overdose deaths have occurred before, at the immediate exposure, and the longer-term impact throughout 2021. We concluded that there was an initial 70% increase in the first month of high national death incidence from the virus, followed by 20% continued increase through all of 2021 over that prior to the pandemic. We also found an exact reverse relationship with seized drugs during this same time: during the months where pandemic deaths first exceeded 1,000 nationally (April 2020), there was an immediate reduction in the number of drugs seized in Pinellas County by police; since then the seized drugs are still lower than prior to the pandemic. This work is being finalized for submission for publication.

**B3. Additional Methodology Achievements.** In the sections that follow we provide further details beyond the Overall Summary above. Early career investigators are identified in **Bold.** We refer to Phase I as papers and products that respond to the aims of the first 5 years, and Phase II as those responding to the aims of this current funding cycle.

Over this last 5 years, the Center for Prevention Implementation Methodology for Drug Abuse and HIV (Ce-PIM) has made significant advances in developing new methods for implementation science especially regarding HIV prevention. By methods we particularly focus on measurement, modeling, design, testing/evaluation, and frameworks. Ce-PIM was the only NIH center solely devoted to implementation science methodology. We provide examples below of all four of these areas of methodology for implementation, with other examples in later sections. References to published work are presented, noting current or former Ce-PIM mentees with their names in **bold.**

**Developed Cutting Edge Research that Builds the Scientific Methodology Necessary to Carry Out Implementation Research.** Here we summarize key frameworks, models, tests, and measures that support the
next generation of implementation research. This discussion illustrates ways that our methodologic work is changing the way that implementation research will need to be conducted in the future.

As a first example, we have argued that implementation science, to be relevant, must address health and health service equity. The vast majority of published intervention research is based on efficacy and effectiveness trials over implementation. For example, among the 200 or so published papers on intervention research regarding HIV, only 5% involve evaluations of intervention strategies. This limited scientific knowledge, especially when it does not specifically focus on those at most risk (e.g., African American MSM), cannot use the knowledge gained by science to overcome disparities. A proactive stance that focuses on producing scientific equity and focuses on the implementation phase of the NIH research cycle is the only strategy that would rapidly lead to lower disparities.

A second theme that we have emphasized involves the design strategies for scaling out evidence-based interventions to populations or through service delivery systems that differ from those used to establish effectiveness. Scaling out requires the collection of additional empirical data beyond the data used in scaling-up to similar populations or through the same service delivery system. But there are opportunities to conduct research that diminishes the time to re-establishing an evidence basis by borrowing strength with existing data and relying on a sequential mediational model. We are examining a number of applications of this scaling out strategy, including its use in providing PrEP to African American MSM. Aarons, Sklar, and colleagues published the first of several implementation methods papers on “scaling out,” which provides efficient designs for evidence-based interventions to retain their evidentiary status while being delivered to different populations or through different delivery systems than those used in effectiveness trials to establish its evidence. Our approach builds on Tom Cook’s principles of causality to establish the appropriate levels of empirical support required in each of the RE-AIM components to provide convincing evidence. We apply this logical framework to several prevention programs, including those involving the use of pre-exposure prophylaxis (PrEP) for young men who have sex with men (MSM). PrEP has been found to be over 90% effective when individuals adhere to its daily regimen; however, it is nearly ineffective when taken 40% of the time or less. Adolescent MSM, and especially African American young MSM are often unconnected or weakly connected to health systems that typically provide such services. Also, adolescent MSM and African American MSM are minimally represented in PrEP clinical trials. In fact, CDC’s recommendations for more than 1 million individuals to go on PrEP do not include adolescents because they judged the evidence for their use is not sufficient. Furthermore, because many African American MSM have limited contact with the health system, they not only have among the highest rates of HIV, they often do not know that they are seropositive for HIV, and they are not as likely to receive medical care. There are multiple options for alternative methods of delivery of PrEP to these at-risk populations. These include on-demand PrEP, which focuses on taking a pill the day before and the day after unprotected anal intercourse, or three days after sex. Such regimens and delivery systems are being examined in natural experiments, but none have formalized the requirements for scaling out these approaches that are currently off-label.

Model-Based Implementation Decision Support using Agent-Based Modeling (B.4-Training). We have developed one of the strongest programs in training of young investigators in agent-based modeling (ABM), especially through the leadership of senior researcher Dr. Uri Wilensky at Northwestern who is the developer of NetLogo, the most-used ABM suite available. This work is entirely devoted to advancing decision making around HIV prevention, especially the use of PrEP, and implementation of prevention programs in local as well as national settings. Phase II mentee Dr. Wouter Vermeer, research assistant professor, is being co-mentored by Brown and Wilensky, as is mentee Dr. Arthur Hjorth. Both have worked on the first major NetLogo modeling of HIV transmission, HIV prevention programs, and factors that affect their implementation. Phase II mentee Dr. Samuel Jenness at Emory, is leading ABM simulation studies for HIV prevention using EpiModel software that is implemented in R. Phase II mentee Dr. Aditya Khanna, Director of Network Modeling at the Chicago Center for the Elimination of HIV at the University of Chicago, is using ABM to identify effective preventive intervention strategies for HIV in criminal justice system involved Black MSM.

To expand on the use of these methods, Jenness delivered training on EpiModel, attended by Phillips and Birkett, which currently is being used by both Emory and the University of Chicago sites to simulate impact of programs on HIV prevention. Likewise, Vermeer provided training to NIDA Summer Intern Caroline Halsted,
who was hosted at Northwestern in a NIDA Summer Internship. Our group convened and developed a new agent-based model to examine determinants of opioid related deaths in a rural, underserved county in Illinois. Mentored by Dr. Wouter Vermeer, we built this model and examined factors that impacted minority populations through differential access to care. Vermeer also developed a new collaboration with Dr. Suzi Spear, who has been funded to examine implementation factors affecting treatment for opioids in Los Angeles County (NIDA, SC2DA047839). Vermeer and Wilensky also presented on ABMs to the Prevention Science and Methodology Group (PSMG).

A major focus of our ABM work has been to develop standards for replicating and validating simulation models, especially those that were built on different computational platforms. Replication is one of the essential elements of science, and we have made major advances in clarifying how to carry out such replication, building on experiences by Wilensky and colleagues. While the ABM field has fully embraced transparency in presenting its models, the complex, multi-level nature of HIV prevention makes it extremely challenging to replicate models across different platforms. We have made excellent progress in developing procedures for replicating such models, using Jenness and colleagues’ recent model built in EpiModel and translating this by Vermeer and colleagues into NetLogo.[25]

The second fundamental scientific step required of simulation modeling is that the models be validated at various levels, both in terms of the representations the program uses to characterize dynamic elements of HIV transmission, prevention programs (e.g., PrEP and treatment as prevention, TasP), and implementation, as well as checking against emergent characteristics that are predicted by such simulations at local levels. Under the Open Science approach, Vermeer and colleagues have published standards for such validation procedures in order to ensure that such models reflect accurately the underlying processes and observable characteristics of the HIV epidemic.[26]

Finally, Vermeer and colleagues published findings from an extensive simulation study on what it takes to end the HIV epidemic by 2030 in Chicago. This comprehensive program has been shared with Ce-PIM, and we have developed a new NetLogo program that integrates detailed HIV incidence and prevalence data from CDPH, sexual network data from the RADAR qualifying grant at Northwestern, and observational data from a natural experiment on the uptake of PrEP among African American MSM from our colleagues at Emory. Partnering with the Chicago Department of Public Health, who co-authored this paper with us, we carried out more than 2,000 experiments to determine what combinations of implementation targets needed to be met to achieve the goals of 90% reduction in new cases, and assess how well Chicago is meeting these goals. A status neutral approach much stronger than currently being implemented is necessary to meet the Ending the HIV Epidemic goals.[25] More specifically, with more than 2,000 simulation runs that incorporate factors related to PrEP and Treatment as Prevention (TasP), we found that more than 2/3 of these failed to reach the desired 90% reduction in incidence in 10 years. We have presented these interim findings to the Chicago Department of Public Health (CDPH).

The University of Chicago modeling group, led by Khanna with Brewer and colleagues, has published a model for HIV elimination in Chicago emphasizing the Chicago Department of Public Health (CDPH) surveillance data and the findings from Cook County Jail’s population, which emphasizes both PrEP initiation and retention.[35] We are comparing findings from these two complementary models and sharing with CDPH.

**Implementation Research Designs.** The 2017 publication in the Annual Review of Public Health[84] represents the first published large taxonomy of implementation research designs. This paper, which has 18 authors, is a major product of an NIH meeting held on implementation designs, chaired by Brown. It includes a wide range of implementation examples, including several focused on HIV prevention and substance misuse. Even prior to publication, this paper has been downloaded some 400 times, and it has more than 200 citations.

The chapter by Landsverk et al., in the Brownson et al., second edition book, Dissemination and Implementation Research in Health[103], is a comprehensive review of implementation designs and examples that draws on the ARPH paper described above. This book is used as the major text in implementation science courses, including a Reading Course on Implementation Science that Ce-PIM has developed and now engaged more than 200 faculty and staff at Northwestern. The new chapter on implementation designs in the third edition of this book,
Measurement and Monitoring Systems for Implementation Science. This work continues a long line of research that Ce-PIM investigators and colleagues have developed to measure and monitor implementation strategies, as well as their progress and outcomes, particularly those focused on the Stages of Implementation Completion (SIC). A set of three papers in Implementation Science$^{87,93,104}$ developed new approaches to measure and monitor implementation. All these papers address major challenges in building a science of implementation, that of obtaining accurate, reliable, and cost-effective measures of the implementation process and output. These measures can then be used to monitor, provide feedback, and inform decision making to improve the quality, quantity, and speed of implementation. We describe these themes below.

Automated Mapping of Implementation Stages. A major challenge in implementation research is the intensity of effort required to accurately assess relevant measures, especially assessing key qualitative, quantitative, and timing of implementation components and characteristics. We have addressed this by introducing low burden and unobtrusive measures wherever possible. The paper by Wang et al.,$^{95}$ lays out a new technology for automated monitoring of the implementation process based on notes that implementation brokers routinely provide in the course of their work. This technology is based on advanced text mining procedures to first scrub these text records of any personal identifiers and then extract both previously identified key words as well as relevant free text words that discriminate between implementation stages. These extractions for every note are then developed into a classifier based on supervised machine learning (support vector machines). The final result from this procedure is to provide probabilistic assessments over time of which stage of implementation is activated. We have tested out this technology on implementation broker field notes of the CAL-OH randomized implementation trial of two implementation strategies tested head to head (Brown et al., 2014). We have included in the discussion of this paper issues that show how such automated measurements are applicable to HIV prevention, particularly around prioritizing partner notifications and testing through departments of public health as individuals become identified as HIV positive.

A Systems Engineering Approach to Characterizing Implementation Strategies. The paper by Czaja and colleagues$^{104}$ presents a novel approach for characterizing the implementation strategies, steps and resources that are needed to deliver an evidence-based intervention. This characterization is based on a new systems engineering approach to implementation science and tackles one of the most challenging areas, to characterize the complex components of implementation strategies so that we can obtain generalizable knowledge. Using 10 of the 12 qualifying grants in the initial funding of Ce-PIM, we conducted surveys and interviews, which were then compared across these qualifying grants. This general approach can be used across diverse evidence-based interventions, service delivery systems, and populations.

An extension of the systems science approach to implementing prevention programs was articulated in a recent publication led by Carlos Gallo.$^{85}$ In particular, formal concepts from systems engineering were incorporated with those of existing implementation science. We articulate a social systems informatics approach to implementation science, and describe how an engineering approach can extend the scientific approach to implementation of an evidence-based intervention.

A Social Networks Approach to Implementation Strategies. Ce-PIM presented the first approach that integrated social network approaches to implementation strategies in the first five years.$^{105}$ In the present cycle of funding, Ce-PIM examined social network characteristics that positively moderated the reduction in HIV risk behaviors among those who had criminal justice and other social determinant challenges.$^{91}$ The analysis of the HOPE preventive intervention, one of Ce-PIM's qualifying grants, is driven by networks on Facebook.$^{95}$ Methodologic issues related to the implementation of eHealth interventions are discussed in a paper led by Li$^{16}$, and statistical modeling issues are described in a paper led by Brown with early careerists Valido and Burnett-Zeigler.$^{86}$

Sustainment Measurement System. Ce-PIM has long held that characterizing and measuring implementation process, progress, and outcomes, requires a multidisciplinary approach. The third set of papers in this series, by Palinkas and colleagues, represents an ethnographic approach to measurement in implementation science.
that complements the systems engineering approach of Czaja and colleagues discussed above. Building on the five-year partnership that Ce-PIM has had with SAMHSA, we developed a NIDA funded R34 grant to support the development of a new Sustainment Measurement System (SMS) that could be used within federal agencies to monitor the movement of their grantees towards sustainment. Sustainment is the least studied phase of implementation, and while funding agencies, such as SAMHSA, have repeatedly required grantees to develop plans for sustainment of their programs after the period of federal funding has ended, these agencies generally have no authority to investigate what actually happens to these programs after their funding has ended. The R34 was developed in partnership with SAMHSA so that a general measurement system would be developed that could be used to monitor progress towards sustainment during the grant period, in time for provide feedback and corrections in course. The framework for this project was published in this article, and based on extensive interviews, we now have a survey instrument that is now being used to assess progress towards sustainment in several implementation research and practice settings. In this cycle, we have completed a series of papers on SMS\textsuperscript{88,90}, which are now being used in diverse settings.

**Measurement Involving Ethical Issues.** We note that Ce-PIM also published one Phase I paper led by Pisani with early investigators Perrino and Gallo\textsuperscript{106}, examining general issues in ethical considerations involved in the use of big data technologies and social media platforms that provide support for the implementation of such technologies. In that paper, we discussed text mining procedures to scrub implementation data to remove personal identifying information. We also discuss best practices for informing individuals who are contacted through digital media, for preventing drug abuse, HIV, or other outcomes. This paper also recognizes the need to address disparities when delivering technology-based interventions, since issues of access and cultural discordance can magnify existing disparities. Including ethical considerations such as those discussed in this paper are impacting our approaches to using phylodynamic data for partner services.

In another realm, Evans and Benbow published a report summary of their conference on ethical considerations of using phylodynamic surveillance of HIV to track transmissions and guide partner services (https://digitalhub.northwestern.edu/downloads/1bff6ec0-af92-48dd-a8e2-d17e4ac4f1ec ). This topic is of major importance for the field, as CDC now funds all public health departments to support reporting and monitoring of these results, referred to as Molecular HIV Surveillance (MHS). Recently, local, state, and federal public health agencies have analyzed MHS data to identify, investigate and respond to growing clusters of newly diagnosed individuals who share closely related HIV genetic sequences, referred to as molecular clusters. Unlike other now-standard surveillance data, the use of MHS data to identify linked molecular clusters raises the possibility that the public, and particularly the criminal justice system, might erroneously infer directionality of HIV transmission.

**Scientific Equity for Implementation Science.** Mensah, Smith, Brown and colleagues provided a framework for conducting rigorous scientific studies to address health and health services disparities through implementation science\textsuperscript{66}. We noted that scientific equity\textsuperscript{100,107}, which refers to the need to collect sufficient scientific evidence to guide the delivery of programs to populations experiencing health disparities, must involve effectiveness and implementation research that focuses on these populations. Too often, research on disparities only addresses epidemiologic risk factors, and while such studies are necessary, they provide no clear evidence of what interventions or what implementation strategies are necessary to deliver programs that can overcome disparities. We examined ways to blend implementation research with community-engaged research. While this paper addressed needs for heart, lung, blood, and sleep research emphasized by the NHLBI, the implementation science resources and trainings in implementation methodology, many conducted by Ce-PIM, are of general use across different scientific fields.

**Identifying Disparities and Diminishing Inequities Due to Systemic Racism.** By systemic racism, we refer to the societal condition wherein advantages, opportunities, and value are structurally allocated based on race and ethnicity through collective practices, mechanisms, behaviors, and beliefs enacted through social systems, in such a way, that reproduces and maintains racial hierarchies. A first scientific task is to study the distributions of inequities. One of Ce-PIM’s major research projects involved our characterization of mediators and moderators of Latino HIV prevalence in the US based on county-level data, led by Benbow and colleagues\textsuperscript{3}. This paper shows that over 95% of counties had higher rates of HIV infections for Latinos compared to the rates for non-Latino whites. The higher disparity for Latinos occurs in counties with less population and fewer Latinos,
and we examined explanations beyond region, poverty, and rurality that have previously been identified. Other work identified at least one contributing reason for such differences. In the previously mentioned mapping review led by Smith and Li to characterize the NIH funding landscape of HIV implementation research, we identified the most dramatic disparity in implementation research was that Latinos were far less represented in HIV implementation research than their population level, a factor in scientific inequities.

In a recent paper led by Murry, with early investigators Bradley, Cruden and Prevention Science and Methodology Group administrator Hanna, as well as other colleagues, a call has been made for re-envisioning, retooling, and rebuilding prevention science to address structural and systemic racism and promote health equity. As described in the paper, for Black Americans, “[t]he environments and conditions created and sustained by systemic racism have been characterized metaphorically as toxic, hazardous, polluted waters Black families swim in as they navigate everyday life experiences.” Social, political, service systems and scientific environments for Indigenous, Pacific Islander, Latino/a/x Hispanic, and Asians are often hostile as well. As steps towards a proposed solution, we begin with a clear statement. For implementation science to have any value, it must embrace equity not only as a stated goal but also in the definition. It is no longer sufficient for the scientific enterprise to document disparities; unlike earlier stages of the traditional translational pipeline (i.e., pre-intervention, efficacy and effectiveness studies), it is only the implementation domain that can reverse these disparities. There is a growing swell of this perspective of “equity,” rather than the limited “equality” theme, so that equity has found residence among implementation scientists, especially prominent in the upcoming generation.

This perspective on reversing the effects of systemic racism should have a prominent place in the theories, practice, and defining scientific paradigms that address the roles of social factors and social determinants on the health of minorities. One key approach would be to elevate the research on the role of institutional racism in health, similar to the approaches that our Ce-PIM colleagues at the University of Chicago have focused on regarding the criminal justice system. Secondly, it is important to expand community voices in framing and understanding how the effects of racism has and continues to be transmitted. Much of prevention science has been built on the successful impact of micro-level interventions on developmental course towards health. These are important but insufficient to overcome historical disparities and need to be complemented by upstream interventions that either directly target, or impede the larger systems that perpetuate racial disparities. We provide an example regarding COVID-19 vaccinations of how tuning preventive intervention strategies to fit the characteristics of minority communities can improve their outcomes.

Another recent paper by Brown, with early career investigator Valido and colleagues, have proposed a general multiplicative implementation strategy that can also increase the population impact of a preventive intervention. This has the potential of reversing historic disparities as well.

**Mediational Modeling Across Multiple Trials.** Mediational analysis is of fundamental importance to implementation science, but there exist several limitations to using this analytic approach. One major area where mediational analysis is important is in combining data across multiple randomized trials to obtain more precise estimates than one can obtain using a single study. The primary reason for combining data across trials, is that mediational analyses in single trials are almost always underpowered compared to their primary outcome analyses of efficacy or effectiveness, and thus combining trial data can lead to mediational modeling with precise enough inferences. While our group and others have conducted mediational analyses by merging multiple datasets into one large datafile (i.e., integrative data analysis or person-level meta-analysis), many times it is not possible to combine individual level datasets. This requires that we combine data using summary information obtained from conducting mediational analyses on each of the separate trials. Led by early career Huang, we developed a new method to combine such summary mediational findings and implemented this in R. This method was used to synthesize findings from three drug abuse preventive trials that used Familias Unidas for Hispanic families, where populations differed in level of risk across the trials (from universal, to selective, to indicated). These analyses demonstrated a moderated mediation effect, where mediation of youth substance use outcomes only occurred through changes in parent-child communication when the quality of parenting was poor at baseline. Such mediational modeling will be used to combine data on medication adherence to PrEP as well as examining the quality of training, supervision, and fidelity in implementing evidence-based interventions. We recently applied this method to combining data across multiple trials of a virtual reality intervention.
Expanding the Implementation of Evidence-Based Parenting and School-Based and Parent-Based Programs for Preventing Adolescent Drug Abuse and Sexual Risk Behavior. In the first five years of Ce-PIM funding, we partnered with several research groups that were conducting parenting programs that addressed the needs of minority populations, including the Familias Unidas preventive intervention for Hispanic populations, with publications led by early careerist Estrada\textsuperscript{58} and Murry's Strong African American Families, as well as parenting programs for high-risk youth and families, including Dishion's Family Check Up and its extensions on childhood obesity led by Smith and St. George\textsuperscript{76}, and Sandler's New Beginnings Program, with a paper led by Gallo\textsuperscript{89}. With the strong evidence base that these programs have had on preventing adolescent drug abuse and reducing HIV sexual risk, and their successful use in NIDA funded implementation trials, including the CYDS trial of Hawkins' and Catalano's Communities that Care, led by early careerist Spear and co-authored by Mendon\textsuperscript{89} and Spoth's PROSPER implementation trial, there is a growing consensus that such programs should be expanded and implemented on a wide scale to families in the US.

A major opportunity for such large-scale implementation has been the delivery of such programs through primary care, as parents are positively included to listen to advice from pediatricians about their child's health. A forum at the National Academies of Medicine recognized that the Affordable Care Act health care reform in the US could provide a major access point to increase the delivery of such evidence-based parenting programs, if such programs were determined by the US Prevention Services Task Force to be of an "A" or "B" level of quality of evidence. As a Phase I activity, early career Cruden led a complementary paper on the implementation of prevention programs through primary care, by proposing new approaches to sustaining prevention programs through an integration of public education and public health\textsuperscript{110}. As another Phase I publication, we also published an overview article\textsuperscript{111} to the special issue of the Journal of Preventive Medicine.

Smith, St. George, and Prado (2017) published a Phase I article on implementation factors more directly involved with the local service delivery agency. They studied the effects of a shared component of parent training, positive behavioral support, on childhood obesity, which is often reduced even if not directly targeted by these preventive interventions. In a second publication, Smith and Polaha\textsuperscript{78} describe the application of the EPIS framework and the Proctor et al. taxonomy to two pilot trials testing the integration of the Family Check Up, a Ce-PIM Phase I qualifying grant, into primary care. In it, they present a real world example of the use of Implementation Science methods to evaluate the integration of an evidence-based family intervention into primary care.

Addressing HIV Prevention Efforts in Urban Environments. At the beginning of the current funding period, we began working across the Northwestern, University of Chicago, Chicago Department of Public Health, and Illinois Department of Public Health sites to coordinate activities involving HIV prevention. Preliminary to Year 06, Benbow and Schneider collaborated on a publication that focused on the potential use of HIV nucleotide sequencing of HIV infections as a novel approach to reducing HIV infections\textsuperscript{9}. These researchers found that younger, male, non-Hispanic black, and MSM were more highly connected than other people. Furthermore, "HIV transmission does not occur primarily within one's region of residence; rather, people move about the city when engaging in high-risk behaviors." The conclusion of this work to focus prevention efforts for young, African American MSM beyond traditional geographic targeting is consistent with other research conducted by Mustanski and early career colleagues Morgan, Birkett, Janulis, and Newcomb, in which young African American MSM were found to have fewer venues to meet partners and often engaged in sex with older MSM, who were more likely to have HIV\textsuperscript{112}. The applications of phylodynamic analyses are just now reorienting the focus of Chicago's approach to HIV prevention and treatment interventions. A more extensive examination of how HIV sequence data reported to state and local health departments can be used to better target and inform public health interventions is currently being conducted through a CFAR administrative supplement received by Benbow in the fall 2016. One of the aims of the supplement is to host a consultation that brings together national and local expertise, including, bioethics, public health, phylodynamics researchers, policy/legal experts, community representatives, and health departments to develop a report outlining ethical considerations and recommendations for the use of molecular HIV surveillance data for public health action. Also, a submitted grant led by Schneider with Benbow as co-Investigator, would support new simulation modeling of the use of phylodynamic information to prioritize local department of public health implementation strategies focused around identified growing molecular clusters. We also plan to submit a new application for CFAR pilot awards.
that would apply the EPIS implementation model that would involve HIV testing and linkage to care interventions.

Almirol, McNulty, Schmitt, et al., (2018) examined gender differences in diagnosis and linkage to care (LTC) in the Expanded HIV Testing and Linkage to Care (X-TLC) program within healthcare settings. Data were collected from 14 sites on the South and West sides of Chicago. Multivariate logistic regression analysis was used to determine the differences in HIV diagnoses and LTC by gender and HIV status. From 2011 to 2016, X-TLC performed 281,017 HIV tests; 63.7% of those tested were women. Overall HIV seroprevalence was 0.57%, and nearly one third (29.4%) of HIV-positive patients identified were cisgender women. Overall, women had lower odds of LTC compared with men (adjusted odds ratio = 0.58, 95% confidence interval 0.44–0.78) when controlling for patient demographics and newly versus previously diagnosed HIV status. Thus, interventions that focus on optimizing entry into the care continuum for AA women need to be explored.

Ridgeway, Almirol, Schmitt, et al., (2018) assessed behavioral risk factors, self-perception of HIV risk, and interest in PrEP linkage among women, men who have sex with women (MSW), and men who have sex with (MSM) who tested HIV negative in an urban emergency department. Women had lower odds of perceiving any HIV risk versus no risk compared to MSM (uOR=0.39, 95% CI 0.18–0.87), while Whites had greater odds of perceiving themselves as high risk compared to Blacks (aOR=0.35, 95% CI 0.13–0.99). Age and self-perception of risk were not associated with PrEP interest, but patients who were objectively classified as “at risk” had greater odds of interest in PrEP than those not at risk (p<0.01). Discordance between HIV risk self-perception and objective risk demonstrates the limitation of relying on patient self-referral for PrEP based on their own subjective risk perception.

Building Measurement and Monitoring Systems for Implementation Science. Berkel, early investigator Gallo, and colleagues report on the mapping of mediational models to examine how the relationship between fidelity of program implementation and health outcomes for youth whose parents participate in the New Beginnings parenting program. New Beginnings, which is designed for divorcing families, has demonstrated long-term benefit on youth’s internalizing as well as externalizing behavior, including youth substance abuse. They developed a theoretical cascade model leading from fidelity and quality of program delivery to parental attendance and home practice competence, and parenting practices as well as child adjustment. This model is complementary to a portion of the sequential mediational model presented in the Aarons and colleagues paper described above. The rigor of the measures of fidelity content and quality in this paper is excellent. Unlike many effectiveness trials, this research program finds clear evidence that content and fidelity have impact on parental engagement and child outcomes, and we attribute this to the high reliability and validity in the human codings of quality and content done in this study. Because human coding is so labor intensive, we have proposed the use of automated fidelity ratings such as we have been conducting using computational linguistics and machine learning.

Preventing HIV Transmission among Women. A Ce-PIM Phase I pilot funded project, with clear Phase II implications, led by Dr. Courtney Cavanaugh mapped the availability of the female condom in 1228 service providers in Philadelphia communities, which include a large percentage of African American women. She found that female condoms are available in less than 1% of these providers, strongly indicating that other forms of HIV prevention, specifically PrEP are of critical importance. Phase I Ce-PIM mentee, has published a Phase II relevant paper on contextual factors related to African American women and HIV prevention (Stewart et. al. 2016). Additionally, the Center for the Evaluation of HIV Prevention in Chicago that Phillips directs works with a community based organization in Chicago that exclusively provides preventive services for HIV-negative cis-women and the extension of this project led by Greene has a focus on HIV prevention through PrEP provision for transwomen.

A funded CFAR supplement to study HIV prevention in African American women, based on the priorities set by our sister TC-CFAR Scientific Work Group, is being led by Dr. Lisa Hirschhorn, who is New Investigator for NIH HIV studies, although she has received extensive support for CDC and other HIV related grants. Hirschhorn has also led the submission of an implementation science evaluation grant application to HRSA for HIV treatment that includes a focus on trans-women. Dr. Gina Wingood*, who is a leading expert on African American and
Latino women and HIV prevention, is a Ce-PIM Scientific Advisor and is providing consultation on a number of our projects addressing HIV prevention for women at high risk of HIV infection.

Using data from the RADAR qualifying grant, Phillips and colleagues\textsuperscript{17}, presented first findings on the knowledge, awareness, and vaccination for meningitis among young MSM. These authors noted that public health professionals have an important role in reducing the large disparities in meningitis and its vaccination that particularly affect African American MSM.

Drs. Christina Dyar (Northwestern University), Heather Bradley (Georgia State University) and Ethan Morgan (Ohio State) have collaborated on cross-cohort analyses of data from two qualifying grants: RADAR (PI Mustanski) and Element (PI Sullivan). This paper uses these cohort data to examine how decreases in substance use absent complete cessation are associated with improvements in mental health among men who have sex with men (MSM)\textsuperscript{113}.

**Integrating Implementation Science with Evaluation and Quality Improvement Programs.** To date, evaluators working in HIV prevention have focused on individual interventions, largely overlooking the complex environment in which these interventions are implemented, including other programs funded to do similar work. The Phase I paper led by Phillips\textsuperscript{114} and colleagues describes our novel approach to adapt the principles and methods of the Empowerment Evaluation approach, to effectively engage with 20 Chicago Department of Public Health funded HIV prevention programs to collect and synthesize multi-site evaluation data, account for systems information, and ultimately build capacity at these organizations to foster a learning-focused community. This work combines milestones of implementation of PrEP programs so that we can construct a monitoring system for implementation.

**Inter-CFAR Implementation Science.** Ce-PIM was instrumental in helping to establish the first Inter-CFAR workgroup on implementation science. This was a collaborative effort with Ce-PIM faculty working with the Northwestern University Third Coast Center for AIDS Research (TC-CFAR) and the Johns Hopkins CFAR, as Ce-PIM faculty Brian Mustanski (co-director), JD Smith (associate director), and Nanette Benbow were leaders of this Inter-CFAR Steering Committee on Implementation Science. A major event conducted by Ce-PIM leading to the establishment of this workgroup was the systematic mapping review, led by Smith and Benbow, of NIH-funded implementation research in HIV over the last 5 years. This massive effort to review the field was accomplished by 11 Ce-PIM members, who attended our Reading Course in Implementation Science. Because of these shared experiences in the reading course, our systematic reached 94% agreement on its coding. A paper is now submitted for publication that describes this review, and our team has made numerous presentations on this work to OAR, to NIH, CDC, and at research meetings around the country.

**New Hybrid and Implementation Trials Designed and Conducted with Ce-PIM Faculty.** We have provided an integral role in the development of 6 implementation and hybrid trials.

1. A major implementation trial was funded during this funding cycle, with the support of Ce-PIM. The Keep it Up! 3.0 HIV prevention trial, led by Mustanski, with Brown, Smith, Benbow, and early career investigator Dennis Li, is in the field where two alternative system deliveries of KIU! are being tested against one another, one is sponsored and conducted by a local Community-Based Organization and the other is via a Direct to Consumer approach.

2. A major challenge in implementation design involves providing enough statistical precision to reliably detect meaningful differences in implementation. A large number of implementation studies are underpowered because of the limited number of sites with which one can test a single or multiple implementation strategies. Brown has worked closely with Egland and other colleagues in Norway to design and then show impact on implementation outcomes in the first international implementation trial of Aaron’s Leadership and Organizational Change for Implementation (LOCI), using a stepped-wedge design.

3. Prado and Brown were funded by NIMH to conduct a randomized hybrid type II trial of an eHealth version of Familias Unidas, delivered to Hispanic families who are attending pediatric clinics. The primary health outcome in this trial is suicide risk behavior, measured using a computerized adaptive test developed by Robert Gibbons.
With careful planning this type II trial has sufficient power to detect both effectiveness and implementation outcomes.

4. A comprehensive stepped-wedge/rollout trial of a Collaborative Model of Care, was designed by Ce-PIM to test its impact on depression and its implementation outcomes in 11 primary care sites within Northwestern Collaborative Behavioral Care Project (CBHP). This study is a stepped-wedge hybrid type 2 randomized roll-out effectiveness-implementation trial of the Collaborative Care Model in 11 primary care practices affiliated with Northwestern Medicine. Using a sequential mixed methods approach, we are assessing key stakeholders’ perspectives on barriers and facilitators of implementation and sustainability of CBHP. The speed and quantity of implementation activities completed over a 30-month period for each practice is assessed using the Stages of Implementation Completion. Economic analyses are being conducted to determine the budget impact and cost offset of CBHP in the healthcare system. The design of this hybrid type II trial is described in a publication by Smith, Fu, Carroll, Burnett-Zeigler, and colleagues.

A related paper by Fu, Carroll, Burnett-Zeigler, Carlo, Smith and colleagues provides new methodology for examining conditions involving patient “failure” to enroll in a new implementation program. Many implementation science projects ignore patients’ voices relative to those from health delivery systems and therefore provide little information about the “pull” of an intervention along with its implementation approach, focusing almost exclusively on the “push” side. Using the new Consolidated Framework for Implementation Science (CFIR) 2.0, patient voices are much more prioritized than the earlier version. We coded implementation barriers in interviews with patients who declined participation or were lost to follow-up after accepting a program referral. We identified multi-level linkage barriers to the Collaborative Care Model (CoCM) for depression and anxiety in primary care and discuss implementation science strategies to improve reach of CoCM and behavioral health resources in primary care.

5. In the SMART trial of an eHealth sequence of interventions for adolescent MSM to reduce HIV risk behavior, Ventuniac, Li and colleagues report on key determinants at the beginning of this trial. Like its name, this randomized trial uses a SMART design to intensify the intervention for those whose behavior remains risky.

6. Brown has collaborated with Peter Wyman at the University of Rochester on the design of a follow-up hybrid type II trial of the Wingman Connect preventive intervention for suicide prevention, conducted in the US Air Force. This pending application to NIMH follows on the successful efficacy trial of Wingman connect delivered to new Airmen. Special analytic modeling was developed to examine how the degree of training that occurs at each base over time in a stepped-wedge design relates to monthly reports of suicide attempts. A special design component is included in this trial to account for one potential confounder in stepped-wedge trials:

Methodology for Testing. Two innovative approaches to implementation testing have been developed this year. The first involves a large expansion of what we have termed rollout trials. These trials randomly assign large units, such as clinics to the timing of when an implementation strategy begins. They include stepped wedge designs, which are currently being used in Norway to test the LOCI leadership program in both adult and child mental health clinics (Egeland et al., 2019). There are many variations in rollout designs, and Brown has been developing an R Shiny program that is being used to display alternative assignment patterns in grant proposals currently under review at NIH. Among the variations in these implementation designs are ones that have multiple components targeting different levels, such as the clinic and clinician; have installation of different strategies over time, such as a phase-in of a sustainment period; and have some components have a head-to-head comparison of different strategies tested at the same time. The supplement to Ce-PIM supported by NIDA and the Office of Disease Program (NIDA, P30 DA027828-S3) is continuing to address the design and power calculations for implementation designs that involve interactions among sites, such as one would obtain with learning collaboratives. Secondly, we have developed rollout designs that can answer the hypothesis that implementation of a single implementation package is likely to improve over time and therefore have faster, deeper, and more effective implementations occurring with later assigned clinics compared to earlier ones. These criterion-based implementation hypotheses are being tested in a recently funded NIH grant led by Dr. JD Smith (J. D. Smith et al., Accepted).
Tools. We continue to add components to a general program to calculate statistical power for implementation trials that use roll-out designs described above. This design class includes the stepped-wedge design as well as a large number of other cousins, including a head-to-head randomized roll-out implementation trial, and a single implementation roll-out study where we hypothesize that implementation will be stronger for later-randomized sites compared to those randomized early in the process. Currently there is no general purpose computational program for such designs, and our perusal of the literature has found that three important sources of variation are often ignored or inadequately dealt with in others’ power calculations. These are variations in site, variations in time, and interactions among sites, such as one finds in designs that involve learning collaboratives. Our program, written in Shiny R, involves statistical simulation of complex, multi-level models and has been presented by Brown at the Ending the HIV Epidemic (EHE) conference recently held in Chicago (C. H. Brown, 2019). A paper is being prepared so that this program can be made available to others in the field (J.D. Smith & Brown, Planned).

Methodology for Measurement. Bolded names identify early career investigators supported by Ce-PIM during this funding cycle.

Benbow and colleagues in our UC Irvine collaborative site, published a paper jointly authored by public health leaders regarding innovative ways to monitor social media for local trends in HIV prevention (N. Benbow et al., 2020). Benbow and colleagues also published two papers on ethical uses of phylogenetic HIV surveillance data (Dawson et al., Accepted; Galletly et al., 2019) based on a national meeting that Benbow had organized in 2019.

Palinkas, Spear, Mendon, and colleagues, including several at SAMHSA, have continued to publish on the sustainment measurement system (SMS) (Palinkas, Mendon, et al., 2019; Palinkas, Spear, et al., 2019), which is being evaluated for predictive validity across HIV prevention, drug abuse prevention, and early mental health preventive interventions funded by SAMHSA. This instrument has excellent psychometric properties and is being distributed to researchers across the country and is being used in NIH applications.


Gibbons, Smith, and colleagues published the first use of computerized adaptive testing (CAT) for screening individuals in the criminal justice system (Gibbons et al., 2019), one major service sector that is not only experiencing high rates of HIV and drug use, but also disproportionate COVID-19 infections. It is also experiencing great disparities as African Americans, Latinx, and the poor are far more likely to be incarcerated compared to others. Our collaboration with Robert Gibbons and the Cook County Jail, the largest mental health treatment facility in the country, involved rapid and standardized assessment of mental health status and substance misuse in the Cook County Bond Court. Such measures were accepted by both system and arrestees and not only save time but they remove the potential for biases in the existing face-to-face assessment. Such tools could be used both in urban jails, where the incarceration population is very large, and in rural jails where there is limited or no assessment of the needs of the inmate population due to limited resources and trained staffing. CAT is also being used as the primary measure in a large group level effectiveness trial of a depression and suicide prevention program for the Air Force, led by Peter Wyman with Hendricks Brown serving as the lead methodologist and Gibbons providing access to the CAT.

Two additional areas for measurement focus on the development of implementation logic models and implementation mapping. These papers have been led by former mentee Smith (J. D. Smith, Li, D., & Rafferty, M.R., Under Review) and current mentee Li (Li et al., Accepted). Both of these guides have been used in the past for efficacy and effectiveness trials, so transferring these guides to the implementation world helps the field formalize how implementation strategies target specific barriers and facilitators on the one hand, and how their planned mode of action are intended to produce both implementation outcomes and health outcomes for the target population.
In Li, Benbow, Keiser, et. al., (2022) we applied the newly updated CFIR 2.0 in a systematic review of implementation determinants related to HIV pre-exposure prophylaxis, including those pertinent to those who are HIV negative but at risk. Recommendations for using CFIR 2.0 were developed through this process. Coded findings from this review were developed into a publicly accessible data dashboard for use by other researchers and implementation practitioners.

**Methodology for Modeling.** Bolded names identify early career investigators supported by Ce-PIM during this funding cycle.


Vermeer has led a comprehensive paper to examine the replicability of ABMs built using different platforms. Successful replication of ABMs instantiated using different platforms is a critical requirement for ABMs to be used in decision making. Vermeer, partnering with our former Ce-PIM mentee Sam Jenness replicated the extensive paper that compared 10 alternative definitions of reach based on CDC’s general guidelines of who is appropriate for PrEP using EpiModel (Jenness et al., 2016). Parts of the replicated model, which was instantiated in NetLogo, used identical parameters and distributions. However, the two models differed considerably on one key aspect. Using a model of sexual networks that was more in line with modern ABMs, the NetLogo replication deliberately tested whether varying this critical part would result in a different prediction for incidence of HIV among each of the 10 different interpretations of the CDC guidelines. We found that the numerical incidence rates were quite different, but more importantly, there was almost perfect correlation between the two models ($r = 0.97$) so the conclusions of which interpretations of the guidelines would be better or worse were identical. In addition to the detail on how to check for numerical agreement, distributional agreement, and relational agreement in ABMs, this paper exemplifies how to document such models so that there is enough information available for full replication. Thus it contributes as a protocol for how to conduct ABM development and simulation experiments in transparent fashion.

**Systematic Reviews and Methods Overview Papers.**

Two overview papers on methods for implementation science have been published. Smith and colleagues reviewed quantitative methods (J. D. Smith & Hasan, 2019), and Brown presented a view of how implementation measures, modeling, and design can contribute to the future of improved mental health services by incorporating artificial intelligence and personalized interventions (C.H. Brown, Accepted).

We published the first overview paper on designs for implementation and hybrid studies led by Brown with early career investigators Cheung and Cruden. This provided a classification of non-randomized as well as randomized designs used in implementation. It also described a framework for building a consensus between implementation researchers and community and institutional stakeholders to obtain a design that meets all of these needs.

Ce-PIM published the first mapping review of NIH funded implementation research on HIV over the last 5 years. This included co-authorship by 3 former mentees and 3 current mentees; Smith (first author, former mentee), Li, Gallo, McNulty, Phillips, and Birkett along with two other mentees not formally funded on this grant, Rafferty and Rao. Until this paper appeared, there was no real standard of what constituted implementation science research in the HIV field. One finding was that many of the projects had the capacity to conduct more implementation science work in their funded projects, but among the minority that did, the work was very limited, what we termed pre-implementation research. This massive effort to review the field was accomplished by a total of 11 Ce-PIM members, who attended our sponsored Reading Course in Implementation Science in 2019. Because of these shared experiences in the reading course, our mapping review reached 94% agreement on its coding.

**Impact of the COVID-19 Pandemic on Overdose Deaths.** As part of our COVID-19 supplement, we
examined in detail the immediate as well as lasting impact of the pandemic on overdose deaths in Pinellas County, Florida. Since the start of the pandemic until the end of 2021, the number of people dying from an overdose as a primary cause of an accidental, suicidal, or undetermined death is 40% higher than the previous period beginning January 2019 (27% to 55% increase in a 95% confidence interval, $p < 0.00001$). We also examined whether there was an initial increase in the first month of high national death incidence from COVID-19 (comparing the change from March to May, 2020), as well as afterwards. There was a stable rate of 41 causal overdoses per month before Covid followed by an abrupt 70% increase to 60 per month with a gradual more moderate decline in the death rate to 51 per month that still remains elevated compared to before the pandemic. This pattern of an abrupt increase in overdose deaths at the time when the pandemic reached the county, followed by a continued elevated rate is replicated for all the following major types of overdoses: fentanyl and its analogues, amphetamines, cocaine, anxiolytics, and alcohol. During this time heroin deaths decreased dramatically. We also examined the consequences of the COVID-19 pandemic on seized drugs by police from 2018 to 2021. Here we find the exact opposite changes from overdose effects: as soon as the pandemic appeared there was an immediate reduction in all types of drugs seized, and since then the numbers of seized drugs remains lower than prior to the pandemic.

National and International Service to the Field.

**Third Coast Center for AIDS Research & ISCI.** Northwestern’s and University of Chicago’s Center for AIDS Research, directed by Dr. Richard D’Aquila and colleagues, was refunded, along with a supplement specifically for implementation science, titled “Implementation Science Coordination Consultation and Collaboration Initiative ISCI” (P30 AI 117943), co-led by Mustanski, Benbow, Smith, Li, and Brown as Co-Investigators. A large portion of Ce-PIM’s service effort this year involves the presentations, coordination, consultation and collaboration on ISCI. ISCI serves as a national resource through coordination and technical support for the use of Implementation Science within the national Ending the HIV Epidemic (EHE) initiative. The two overarching goals of ISCI are to maximize the value of implementation science (IS) in EHE: (1) support high-quality IS in EHE research projects by providing technical assistance from experts on IS designs, strategies, frameworks, measures, and outcomes and (2) create opportunities for local knowledge from each project to become generalizable knowledge by encouraging the use of shared frameworks, harmonized measures, synthesis of data across projects, and cross-project collaboration. Through continued funding for Years 3 and 4, ISCI has four specific aims: (1) Synthesize HIV-specific IS knowledge to improve the integration and use of implementation research methods and findings by HIV researchers and practitioners. Through our continued systematic literature reviews and consultation with the IS Hubs, other HIV IS experts, and a newly formed Community and Implementation Practice Committee (CIPC), we will establish a method for defining best practices for HIV IS and develop interactive tools for researchers to better adopt and integrate IS concepts. (2) Inform, design, and pilot a national resource consortium for implementation research. With the Hubs, we will engage local partners and develop and execute a protocol for a multisite implementation research study as proof-of-concept for national-level HIV IS infrastructure. (3) Enhance and implement our systems for collecting, analyzing, and reporting on data elements shared across EHE grantees. (4) Provide technical assistance and create and disseminate resources for academic, community, and federal stakeholders within EHE.

Progress to date includes the following: In June/2022, ISCI were editors and published a special JAIDS supplement including 27 articles on HIV implementation research and presented a selection of manuscripts in a satellite symposium at the AIDS 2022 in Montreal. Included in this special issue was the first manuscript of the systematic review of PrEP determinants led by Dennis Li and co-authored by Benbow, Mustanski, and Smith among others. In collaboration with other academic centers, ISCI is conducting a multi-site pilot of a Rapid Status Neutral approach scheduled to begin early winter/2022. ISCI has developed a visualization tool (the dashboard) to disseminate implementation determinants and strategies derived from a PrEP mapping review, what is relevant to both researchers and practitioners. This will be expanded to include HIV testing and linkage/engagement in care from on-going mapping reviews. The dashboard and other IS tools and resources can be found in ISCI June release of their new website (hivimpsci.org). Additionally, ISCI faculty have conducted key informant interviews and a first stage Delphi process to identify criteria for best practice implementation strategies.
Dennis Li and Nanette Benbow (co-PIs) were funded for a FY2021 NIH EHE administrative supplement titled “Configurations of Linkage, Engagement, And Retention Strategies for HIV (CLEARS-HIV)” to conduct a mixed-methods, cross-sectional study to characterize discrete strategies and contextual determinants of HIV care engagement programs currently being used by Chicago Department of Public Health (CDPH)-funded HIV testing providers and HIV care agencies. Guided by the ERIC implementation strategy taxonomy and the Proctor et al. framework for specifying and reporting strategies, the project is in the process of identifying and describing the components of each agency’s care engagement programs to determine which configurations of strategies, determinants, and other characteristics are associated with better reach of HIV care using coincidence analysis. Results from this study, expected in March/2023 will directly inform local planning of CDPH’s HIV services and best practices among funded agencies, and nationally, will support tailoring and scale-out of care engagement programs that are crucial to achieve EHE goals.

On-going collaboration with the CDPH, and CLEARS-HIV helped inform the proposal “Promoting Sustained Viral Suppression through Implementation of an Adapted Evidence-Informed Low-Barrier Care Model in a System of HIV Primary Care Clinics,” in response to NIH’s RFA-AI-21-024, Multidisciplinary Treatment Approaches to End the HIV Epidemic. In August/2022 Dennis Li and Nanette Benbow (MPIs) were funded for this project whose primary goal is to harness implementation science to develop and evaluate a local system-level LBC implementation plan to facilitate retention in care and viral suppression for clients with complex needs.

**New NIDA Center Funding.** With the recent push by NIDA to address overdoses through the HEAL Program, Brown and colleagues have shifted their work from Ce-PIM’s P30 mechanism to two newly funded centers.

**Newly funded NIDA Center for Dissemination and Implementation at Stanford.** Led by Mark McGovern at Stanford, this new P50 grant addresses core implementation research around critical needs for addiction and overdose. Brown serves as co-director of the Research Core, along with Lisa Saldana, and he also directs Research Project 1, which is examining a model-driven decision support system in three distinct counties; Pinellas County, FL, Vermilion County, IL, and Santa Clara CA. With the move of Dr. Sara Becker to Northwestern, we now have two of the three P50 projects led by Northwestern faculty with expertise in implementation science.

**Newly Funded NIDA Research Adoption Support Center (RASC).** The RASC is a U2C Center, also led by Mark McGovern, that is part of the HEAL Data2Action (HD2A) addressing both substance use disorders and pain. Both Brown and Becker serve as Multiple PIs on this project, which provides implementation support for HD2A innovation grants.

**Implementation Methodology Training and Mentored Training (B.4-Training).**

Throughout this Ce-PIM funding cycle, we have directly financially supported the following early career investigators at Northwestern University: JD Smith, Wouter Vermeer, Dennis Li, Carlos Gallo, Gregory Phillips, Michelle Birkett, Christina Dyar, Arthur Hjorth, and Can Gurken as well as Nanette Benbow, (not counted as early career investigators). We also financially supported Moira McNulty, University of Chicago, Russell Brewer, University of Chicago, Samuel Jenness and Heather Bradley, Emory, and Akihiro Nishi, UCLA. For a full list of mentees please see Table 4.

Ce-PIM, the Shirley Ryan AbilityLab, and the Northwestern CTSA NUCATS D&I Program, co-organized a Reading Course on Implementation Science for the 4th consecutive year. Led by Rafferti and Li, and facilitated by Villamar, and Ce-PIM mentees Carroll and Knapp, this reading course builds on the previous course by extending invitations to senior and early stage investigators from Lurie Children’s Hospital, the Shirley Ryan Abilitylab, the University of Chicago, the University of Illinois at Chicago, and sponsored trainings fellows of NUCATS and Northwestern’s Feinberg School of Medicine. Attendees volunteered to co-lead at least one discussion of their assigned break out groups. There are yearly iterations of the reading course that rely primarily on the Dissemination and Implementation Research in Health by Brownson, Colditz,
and Proctor, and highlighted recently published peer reviewed publications from experts in the field of implementation science as examples.

Engaging with other researchers to expand implementation research.

All of the following early investigators at Northwestern University were funded: JD Smith, Wouter Vermeer, Dennis Li, Carlos Gallo, Ashley Knapp, Allison Carroll, Emily Fu, Kathryn Macapagal, Gregory Phillips, Michelle Birkett, and Nanette Benbow (not counted as an early career investigator).

Northwestern’s CTSA NUCATS D&I Program. Ce-PIM continued it’s relationship with Northwestern’s CTSA through the Dissemination & Implementation (D&I) Program supported by Northwestern’s Institute for Public Health and Medicine (IPHAM) and Northwestern’s Clinical Translational Science Institute (NUCATS). The D&I Program brings together Ce-PIM faculty Brown and Center for Community Health (CCH) to promote dissemination & implementation of evidence-based care & programs to clinical and community stakeholders. The program has proposed to achieve these goals through 1) Training and consultation for academic and community partners on principles of designing and evaluating for D&I and 2) Utilizing existing networks (e.g., practice-based research networks) as a vehicle for disseminating evidence-based interventions & programs. Ce-PIM and the D&I program co-organized a reading course on Implementation Science and began planning a Dissemination and Implementation Research workshop with collaborators from the University of Illinois at Chicago CTSA. Ce-PIM faculty Brown, Li, Rafferty, and Carroll offer consultation service that would service community stakeholders and academic researchers in the application of D&I principles and methods in research applications.

Disseminating Research Findings on HIV Prevention, Drug Abuse Prevention, and Implementation Science to a Broad Audience. Throughout this current Ce-PIM funding cycle, we published 144 scientific papers that acknowledge Ce-PIM, and made 97 scientific presentations (see Tables 1 and 2). To date we have supported 36 early career investigators including 7 currently funded on Ce-PIM, 4 currently funded on K-awards, and 3 on diversity supplements, including Ce-PIM’s own diversity supplement for Brewer (see Table 3).

Prevention Science and Methodology Group Virtual Grand Rounds: We have hosted a total of 170 virtual grand rounds through the Prevention Science and Methodology Group (PSMG), with 159 of these presentations currently available on the web (http://cepim.northwestern.edu/psmg-archive/) as part of our commitment to providing open access to as many of these presentations as we could obtain permission. These presentations aim to reach, teach, and inspire innovations in Prevention Science and Implementation Science methodology, particularly in the fields of implementation science, HIV prevention, and drug abuse prevention. Membership is free and informal but includes several benefits: access to live weekly presentations, weekly newsletter, and networking opportunities with leaders in the files of implementation science and methodology, prevention research, and innovative statistical methods. In Year 09, the PSMG virtual grand rounds presentation series featured an 11-part series titled, "Bringing the Best of Dissemination and Implementation Science to Address the Opioid Epidemic", organized by our colleague Dr. Mark McGovern. PSMG also included a mini-series on mechanisms of implementation science, systems science methods, and a series titled “Mixed Up: Modeling for Context,” in response to this year’s Office of Disease Prevention/NIDA supplement to Ce-PIM (please refer to Table 1). In the past year, archival presentations have been played 2,993 in 59 countries.

The Prevention Science and Methodology Group (PSMG) now has 1400 members. PSMG has continued its outward expansion with an increasingly public-facing online presence on the following platforms: the Ce-PIM website, a Vimeo account (a video sharing online platform), a MailChimp listserv, Zoom-hosted webinars and meetings, and Twitter account’s for PSMG and Ce-PIM. We continue making meaningful contact with our community using our Vimeo account, PSMG and Ce-PIM twitter accounts, and our presence has continued to grow during this reporting period.

PSMG launched its own Twitter handle in February of 2018, and currently has amassed a total of 889 followers. The twitter account is used to promote the presence of PSMG in social media, announcing upcoming presentations and promoting PSMG membership, announcing public access to past PSMG
presentations in our Ce-PIM website and Vimeo account, enhancing dialogue and collaboration between researchers during and after virtual grand rounds, as well as promoting other Ce-PIM products among our growing network of members and followers.

In August 2022, PSMG partnered with The Center for Dissemination & Implementation At Stanford (C-DIAS) to host the Virtual Grand Rounds. C-DIAS is NIDA P50 Center of Excellence (1P50DA054072-01A1). The intent of this partnership is to present current research in dissemination and implementation (D&I) in addiction treatment, or cutting-edge D&I methods applicable to addiction, prevention and treatment. The joint C-DIAS/PSMG sessions will be held twice monthly and presenters will include C-DIAS faculty, trainees or affiliates. In Fall 2022, C-DIAS Director, Mark McGovern, and Co-Director, Helene Chokron Garneau, presented “C-DIAS, the Center for Dissemination & Implementation At Stanford: A new NIDA P50 Center of Excellence”. This presentation introduced the new Center, its mission, structure, as well as four research projects.

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