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Drug and Alcohol Dependence 217 (2020) 108336

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Health economic design for cost, cost-effectiveness and simulation analyses in the HEALing Communities Study

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ARTICLE INFO

Keywords:
Opioid use disorder
Overdose
Economic evaluation
Cost-effectiveness
Simulation
Helping to end addiction long term
HEALing Communities Study

ABSTRACT

Background: The HEALing Communities Study (HCS) is designed to implement and evaluate the Communities That HEAL (CTH) intervention, a conceptually driven framework to assist communities in selecting and adopting evidence-based practices to reduce opioid overdose deaths. The goal of the HCS is to produce generalizable information for policy makers and community stakeholders seeking to implement CTH or a similar community intervention. To support this objective, one aim of the HCS is a health economics study (HES), the results of which will inform decisions around fiscal feasibility and sustainability relevant to other community settings.

Methods: The HES is integrated into the HCS design: an unblinded, multisite, parallel arm, cluster randomized, wait list–controlled trial of the CTH intervention implemented in 67 communities in four U.S. states: Kentucky, Massachusetts, New York, and Ohio. The objectives of the HES are to estimate the economic costs to communities of implementing and sustaining CTH; estimate broader societal costs associated with CTH; estimate the cost-effectiveness of CTH for overdose deaths avoided; and use simulation modeling to evaluate the short- and long-term health and economic impact of CTH, including future overdose deaths avoided and quality-adjusted life years saved, and to develop a simulation policy tool for communities that seek to implement CTH or a similar community intervention.

Discussion: The HCS offers an unprecedented opportunity to conduct health economics research on solutions to the opioid crisis and to increase understanding of the impact and value of complex, community-level interventions.

1. Introduction

The U.S. opioid crisis persists with nearly 47,000 deaths attributed to opioid overdose in 2018 (Nana, 2020). Opioid misuse and opioid use disorder (OUD) have multiple and long-lasting economic impacts on individuals, families, communities, and society (Florence et al., 2016; Inocencio et al., 2013; Leslie et al., 2019; Roland et al., 2019; Scavette, 2019; Segel et al., 2019). Despite the demonstrated efficacy of existing evidence-based practices (EBPs) to support treatment and recovery from OUD, only a small proportion of individuals with OUD are identified as

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https://doi.org/10.1016/j.drugalcdep.2020.108336
Received 17 August 2020; Received in revised form 17 September 2020; Accepted 18 September 2020
Available online 3 October 2020

needing treatment, and less than 20 % actually receive recommended services (SAMHSA, 2019; Wu et al., 2016). Reasons for underutilization of these services include lack of screening for OUD by health care and legal systems, insufficient treatment capacity especially for medications for opioid use disorder (MOUD) and documentation of OUD, lack of access and awareness among individuals with OUD about treatment options, and stigma surrounding the use of MOUD (Braithwaite and Nolan, 2019; Jones et al., 2015; McLean and Kavanaugh, 2019). Additional challenges include limited uptake of overdose prevention approaches such as utilization of community-based naloxone distribution (Meisenberg et al., 2018).

The HEALing Communities Study (HCS) is a four-year, multi-site, parallel group, cluster randomized wait-list controlled trial testing the impact of the Communities That HEAL (CTH) intervention on reducing opioid overdose deaths in 67 disproportionately affected communities across four states–Kentucky, Ohio, New York and Massachusetts. The HCS will assess the effectiveness of the CTH intervention, a stepwise community change process that seeks to mobilize HCS communities to implement EBPs in a range of settings, including behavioral health, health care, and criminal justice systems (Oesterle et al., 2018). CTH has three components: (1) a community engagement to facilitate data-driven selection and implementation (Sprague Martinez et al., 2020); (2) the Opioid overdose Reduction Continuum of Care Approach (ORCCA) (Winhusen et al., 2020); and (3) communication campaigns to reduce stigma and raise awareness and demand for EBPs (Lefebvre et al., 2020). The ORCCA itself comprises multiple options within three areas: (1) overdose education and naloxone distribution; (2) effective delivery of MOUD; and (3) safer opioid prescribing and dispensing. More detail on the CTH components and ORCCA EBPs are provided in The HEALing Communities Study Consortium, 2020 and Winhusen et al., 2020.

The HCS is designed to produce generalizable information for policy makers and community stakeholders seeking to implement CTH or a similar community intervention. To support this objective, one aim of the HCS is focused on health economics analysis and simulation modeling to gain information about fiscal feasibility and sustainability that may be relevant to other states and settings. This paper describes the design for the HCS health economics study (HES). The objectives of the HCS HES are to

1 Estimate the economic costs to communities of implementing and sustaining CTH;
2 Estimate the broader societal costs associated with CTH;
3 Estimate the cost-effectiveness of CTH compared with standard practice, measured as cost per overdose death avoided;
4 Use simulation modeling to evaluate the short- and long-term health and economic impact of CTH, including future overdose deaths avoided and quality-adjusted life years (QALYs) saved; and
5 Develop a simulation policy tool for communities that want to implement CTH or a similar community intervention.

The HES is guided by the recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine (Neumann et al., 2016) and incorporates methods from previous health economics studies of interventions to reduce OUD and its consequences, including definitions of the study's perspectives, approaches to micro-costing, and best practices for cost and cost-effectiveness analyses.

There are few published health economics studies of complex, community-driven interventions for substance use disorders. The most relevant are two benefit-cost analyses (Kuklinski et al., 2012, 2015) of the Communities That Care model (Oesterle et al., 2018) from which the CTH was adapted. These analyses used a micro-costing approach to estimate the resources consumed by communities to implement the intervention, including the process for engaging community coalitions, selecting and implementing a menu of EBPs, and ongoing training and technical assistance. Economic benefits were estimated for a sample of adolescent participants and compared with the costs, ultimately demonstrating a positive economic value (i.e., positive net benefits) for the intervention implementation.

We will follow a similar approach to costing the multilevel/multisystem intervention in the HCS. We will estimate the resources needed to engage community coalitions, to support communities selecting and implementing EBPs, and to conduct ongoing training and technical assistance in service to those EBPs. Our planned analyses, however, differ in important ways. First, our primary goal is to estimate the cost-effectiveness of CTH with respect to opioid overdose deaths and related outcomes rather than to compare monetized benefits with intervention costs to measure economic value. Second, rather than measuring efficacy using outcomes of a cohort of identified individuals who are tracked over time, we will rely on population-level outcomes for the study communities that will be measured in the HCS.

The individual ORCCA EBP components of CTH have a substantial literature assessing their costs and cost-effectiveness. For instance, the cost-effectiveness of MOUD has an established evidence base across a variety of settings and populations, particularly for methadone maintenance therapy and buprenorphine (Barocas et al., 2019; Busch et al., 2017; Dunlap et al., 2018; Gisev et al., 2015; Krebs et al., 2018; Murphy et al., 2019; Murphy and Polsky, 2016). Additionally, programs providing naloxone to high-risk individuals and first responders for reducing opioid overdose mortality have also been found cost-effective (Coffin and Sullivan, 2013; Townsend et al., 2020). Notably, there is a lack of literature on the cost-effectiveness of safer opioid prescribing and dispensing programs.

Simulation modeling has become more common in economic evaluation of interventions to address opioid misuse (Barbosa et al., 2020; Briggs et al., 2006). Specifically, it draws information from multiple sources to integrate information on the trajectory of OUD and associated complications with evidence of the clinical and economic impact of public health strategies to inform the best responses to the opioid crisis. Simulation modeling can augment clinical studies by projecting clinical and economic outcomes over long time horizons and can explore outcomes for populations that differ from the ones that participate in clinical studies. Simulation models can also enhance cost-effectiveness analyses conducted alongside clinical trials by improving the measurement of uncertainty around estimates of economic value, examining causal factors, and characterizing alternative scenarios to inform policy (Buxton et al., 1997). Models with longer-term time horizons can capture the multiplicity of outcomes characteristic of OUD, which often has periods of relapse and recovery accompanied by several comorbid conditions (Barbosa et al., 2020; Nosyk, 2020). The HCS presents an ideal platform for developing simulation models through collaboration among research sites and for engaging communities during model development so that model results can be most useful to decision makers.

The HCS offers an unprecedented opportunity to conduct health economics research on solutions to the opioid crisis—solutions that combine a community-level approach with combinations of proven EBPs and communication campaigns. It provides a significant opportunity to answer questions about CTH costs and to evaluate its cost-effectiveness at reducing opioid overdose fatalities. Additionally, the potential for understanding policies that may lead to sustainable changes in opioid use disorder through simulation modeling provides an opportunity for broad impact.

2. Methods

The methods that will be employed in the HCS HES are described below, including a brief overview of the main study design, cost data collection and analysis methods, cost-effectiveness analysis methods, and simulation modeling methods. The protocol (Pro00038088) was approved by a single (Advarra) Institutional Review Board for all sites on October 16, 2019.

2.1. Main study design

The HCS is an unblinded, multisite, parallel arm, cluster randomized, wait list–controlled trial of the CTH intervention implemented in 67 communities in four U.S. states: Kentucky, Massachusetts, New York, and Ohio. Wave 1 communities (n = 34) will implement CTH for 2 years. During this time, the wait-listed Wave 2 communities (n = 33) will not receive any intervention. In Year 3 of the CTH intervention, Wave 2 communities will begin to implement CTH for 12 months. The full effect of CTH on Wave 1 outcomes is expected to occur after the intervention is fully implemented (by the end of Year 1 of the CTH intervention.) Thus, the primary analysis will compare opioid overdose deaths between Wave 1 and Wave 2 communities during Year 2 of the CTH intervention. Communities are defined as towns, cities, or counties; more detail on communities is provided in The HEALing Communities Study Consortium, 2020.

2.2. Cost data collection and analysis

The goal of estimating startup and ongoing CTH implementation costs is to inform other communities outside of HCS about the resources and other investments required to implement CTH, supporting both replicability and sustainability. Importantly, HCS is investigating the effectiveness, cost, and cost-effectiveness of the CTH process and its resulting intervention priorities and implementation in the real world. HCS does not seek to test the effectiveness or cost-effectiveness of the specific evidence-based interventions selected and implemented in combination by each community. As a result, HCS economic results will inform decision makers about what they can expect in terms of cost and cost-effectiveness before initiating CTH, rather than providing generalizable cost or cost-effectiveness estimates for each EBI.

We have adopted a micro-costing approach (Drummond et al., 2015; Glick et al., 2014; Zarkin et al., 2004) that first identifies activities required to implement the intervention and then identifies resources required to perform those activities. Two perspectives guide our study: (1) a community perspective representing community stakeholders investing time and other resources to support the implementation of CTH and (2) a societal perspective that includes both the direct costs incurred by communities to support CTH (community perspective costs) and the additional costs incurred by the health care and justice sectors attributable to CTH. The community perspective reflects the expenditures—including time and other resources—that communities need to invest for startup and ongoing implementation of CTH. The societal perspective reflects changes in societal resource utilization attributable to CTH. The community perspective costs do not include the changes in societal resources attributable to CTH even when their costs are incurred by community stakeholders. The HCS cost perspectives are guided by the principles of the Second Panel on Cost-Effectiveness in Health and Medicine (Neumann et al., 2016), even though they differ from that guidance in one respect. The Second Panel recommends a minimum of two analytic perspectives: the health care sector perspective and the societal perspective. Because cost-effectiveness analyses in public health and medicine frequently address decisions made in a health care setting for which substantial costs will accrue to health care payers and providers, the health care sector perspective is prioritized as it is most relevant to those decision-making stakeholders. HCS is a community-based intervention; therefore, we chose to substitute the community perspective for the health care perspective to reflect costs incurred that are relevant to community decision makers. Appendix Table 1[1] illustrates the relevant components for calculating CTH costs from the community and societal perspectives, or impact inventory.

2.2.1. Costs to the community

CTH costs to the community arise from two components: (1) startup investments required to launch the CTH in study communities and (2) costs for ongoing implementation. The main startup cost inputs are related to labor time, including time spent training staff, establishing community coalitions, and interviewing and hiring intervention staff. Other startup cost inputs include facilities (e.g., space for trainings and other pre-implementation activities), infrastructure investments such as computers, and other equipment, licenses and adaptation of purchased software, and purchased services such as trainings. Startup costs associated with CTH are measured in the Wave 1 communities primarily in the months leading up to Year 1 of the CTH intervention, with some startup activities occurring after this period such as additional hiring and initial trainings. For example, some community engagement facilitators were hired before Year 1 of the CTH intervention; however, we still consider initial hires that occurred after Year 1 of the CTH intervention begins as contributing to startup costs because hiring activities were limited by job market forces and institutional human resources hiring capabilities, and yet are still best characterized as resources necessary to "start-up" the intervention. A similar (~6 month) timeframe will be used for Wave 2 communities that will begin startup before Year 3 of the CTH intervention. The startup cost estimates for Wave 2 will be compared with Wave 1 startup cost estimates. Wave 2 startup cost differences may reflect efficiencies from lessons learned in Wave 1 implementation and less disruption from the novel coronavirus 2019 (COVID-19) pandemic.

Ongoing implementation costs of CTH are the costs of activities required to conduct CTH on a day-to-day basis and are also primarily labor/time-related. These activities include community engagement through community coalition meetings and other interactions with community stakeholders and partners; communication campaigns; and training, technical assistance, and other support needed to implement CTH's specific EBPs for overdose education and naloxone distribution, MOUD, and safer opioid prescribing/dispensing practices. Non-labor inputs are similar to the categories for startup costs, including costs for space, transportation, ongoing software support and licenses, software development to support coalitions, contracted services, and other purchased materials.

Labor and non-labor cost inputs for both startup and ongoing implementation costs will be assigned monetary values by multiplying a resource quantity (e.g., an hour of time, a square foot of space, a software license) by an appropriate unit price (e.g., a wage per hour or rental/lease value). Ongoing implementation costs for Wave 1 communities will generally be those incurred in Year 1 and Year 2 of the CTH intervention, and for Wave 2 communities these will be costs incurred in Year 3 of the CTH intervention.

2.2.2. Resource utilization attributable to CTH

CTH is expected to influence resources used by communities as OUD prevention and care services are increased or enhanced and individuals receive more services from providers and other organizations implementing EBPs from the ORCCA. The populations tracked for resource use cost estimation will be those targeted by the EBPs: individuals with an OUD diagnosis or who are receiving OUD treatment, or individuals who receive prescription opioids for pain. Costs associated with these resources are not included in the community perspective costs. Most of the measures of utilization of these services will be derived from secondary data sources (see Table 1). We will estimate the resource utilization costs for each community by multiplying resource units by relevant estimated unit costs.

2.2.3. Cost data measures and sources

Table 1 lists the resources, measure characteristics, resource data sources, and unit cost data sources for CTH. The majority of implementation resources are collected from three sources: 1) surveys of intervention participants and key informants regarding the time spent

[1] Supplementary material can be found by accessing the online version of this paper at https://doi.org and by entering doi: …

Table 1
HCS Communities That HEAL Cost Measures and Data Sources.

Costs to the community			
Resource	Measure Characteristics	Resource Data Sources	Unit Cost Data Sources
Time spent by HCS staff and community stakeholders for startup and ongoing implementation of CTH	Coalition meetings and other community engagement activities; communication campaign, including adaptation to community; training, technical assistance, and other efforts to support CTH EBPs	Participant/key informant, HCS administrative data, document extraction	HCS administrative data, BLS, O*NET
Non-labor resources used for startup and ongoing implementation CTH	Space, transportation, meeting expenses, equipment, software licenses, purchased services	Participant/key informant, HCS administrative data, document extraction	Administrative data, invoices, contracts, Internal Revenue Service mileage rates, published prices
DATA 2000 waiver trainings	For all provider types (e.g., physicians, Nurse Practitioners [NPs], Physician Assistants [PAs])	DEA Active Controlled Substances Act Registrants Database	Published prices for trainings
Academic detailing	Pharmacist-delivered education on safe opioid prescribing to physicians, NPS, PAs	Participant/key informant, HCS administrative data, document extraction	Key informants, micro-costing, BLS, O*NET
Drug take-back boxes	Installations of safe medication disposal units	Participant/key informant, HCS administrative data, document extraction; DEA administrative data	Key informants, micro-costing
Other resource utilization attributable to CTH			
Resource	Measure Characteristics	Resource Data Sources	Unit Cost Data Sources
Naloxone units distributed to communities	Including units distributed to public health departments, or health care providers and distributed by pharmacies	State health agencies, HCS administrative data, IQVIA	Published prices for naloxone kits, micro-costing
EMS runs for opioid-related incidents/ overdoses	EMS runs with and without naloxone administrations	National EMS Information System	Literature-based estimates (e.g., Coffin and Sullivan, 2013; Townsend et al., 2020)
MOUD administered in jails	Including buprenorphine, buprenorphine/ naloxone, methadone, and naltrexone for OUD	Participant/key informant, HCS administrative data, document extraction	Literature-based estimates (e.g., Horn et al., 2020)
Health care utilization for individuals with an OUD or related conditions	All-cause health care use, including MOUD; prescription opioids and other pain medication; ambulatory, inpatient, and emergency care; medical and behavioral health care	Medicaid claims; State Prescription Monitoring Program Databases; CDC's National Syndromic Surveillance Program	Medicaid claims, literature-based estimates (e.g., McCollister et al., 2017)
Criminal activity	Number of arrests by type of crime reported by local law enforcement agencies	Uniform Crime Reporting program	Literature-based estimates (e.g., McCollister et al., 2017)

on intervention activities and other non-labor costs; 2) HCS study data including, for example, numbers of staff hired for intervention roles by job title; and 3) financial documentation, such as invoices for purchased services and materials. To avoid "double counting" resources, the surveys and data analyses separate out costs associated with conducting research from those required to implement the CTH.

In addition to primary data collection, we will also employ administrative data collection for analysis. We will use state prescription monitoring program databases to obtain quantities of buprenorphine prescribed for treatment of OUD and prescription opioids prescribed for pain relief. We will use Medicaid claims data to quantify changes in MOUD, behavioral health treatment, and other health care service utilization. Medicaid claims data will be linked with state Departments of Corrections data to identify the number of linkages to MOUD treatment among individuals released from jail. From this, we will assign costs to these linkages to care activities. To improve generalizability, we will explore supplementing Medicaid data with other sources such as Massachusetts' All Payers Claims Databases (APCDs).

Other data sources include administrative data maintained by state departments of health or public health, the U.S. Drug Enforcement Administration's (DEA) Controlled Substances Act Active Registrants database of DATA-waived providers, the National Emergency Medical Services (EMS) Information System, the U.S. Centers for Disease Control and Prevention's (CDC) National Syndromic Surveillance Program, the Federal Bureau of Investigation's Uniform Crime Reporting program, and the IQVIA Xponent database of pharmacy naloxone dispensing. Similar to the planned analysis of the HCS primary and secondary outcomes (Slavova et al., 2020), data collected from each of these sources will be attributed to specific communities based on the locations of individual residences, of providers, or the service or event specific to the intervention time periods described above.

Wage costs will be based primarily on publicly available data from the Bureau of Labor Statistics (BLS), which provides estimates of national-, state-, and metropolitan area–level average wages by Standard Occupational Classification System and the North American Industry Classification System by quarter and year. We will supplement BLS data with information from the Department of Labor's Occupational Information Network (O*NET) database to better reflect the human capital necessary to support CTH activities. These data sources will allow us to estimate wages representative of the chosen geographical unit (i.e., nation, state, metropolitan area) that are based on occupation and role in HCS. Furthermore, by mapping reported titles/occupations onto salaries reported in the BLS we will streamline the data collection process by avoiding the collection of personal information from community respondents. For materials, equipment, software licenses, subcontracts, and other non-labor resources, the actual reported costs will be used, if available. For resources without a direct expenditure such as meeting space within an agency with accessible conference rooms, we will value the opportunity cost of that space using market rates for similar office rentals in the area, available through online commercial real estate sources such as loopnet.com. Similarly, for travel costs to attend CTH meetings (e.g., by community advisory board or community coalition

board members), we will use mapping tools to determine the distance and time traveled and assign a wage rate per hour of travel time and a federal reimbursement rate per mile.

For MOUD costs we will use the Department of Veterans Affairs' Federal Supply Schedule of Pharmaceutical Prices, which is recommended by the Second Panel on Cost-Effectiveness in Health and Medicine for analyses from the societal perspective (Neumann et al., 2016) and the IBM Micromedex RED BOOK to estimate alternative prices faced by other payers. Estimates of health care service unit costs will be drawn from peer-reviewed literature (see for example McCollister et al. (2017) for estimates related to a substance use disorder treatment population) and applied to units of care, such as inpatient or residential treatment episodes, identified in Medicaid claims data. Alternatively, total health care spending may be calculated directly from Medicaid claims or from estimates averaged across Medicaid managed care organizations to explore budget impact for these payers. The cost of naloxone kits will be based on two sources. Estimates of allowable charges for naloxone in IQVIA-provided dispensed prescription data will be used as a cost for pharmacy naloxone kit distribution. For all healthcare units and medication, we will consider alternative price estimates to reflect different perspectives and uncertainty about costs incurred.

Other published costs or micro-costing (primary data collection and analysis of costs conducted by the HCS team and focused on specific intervention components) estimates will be considered for naloxone distributed by community partners and administered by first responders. Finally, some of the ORCCA EBPs implemented in specific communities may use unique approaches or resources that may not have readily available unit cost estimates in the literature. For example, academic detailing for MOUD prescribing is being adapted specifically for use in the HCS. When appropriate, micro-costing studies of these interventions will be conducted.

We anticipate several types of missing data and nonresponse in primary data collected for the HCS HES. Instruments may not be administered during some periods of time (e.g., early in the study for some community coalitions), and data will need to be either collected retrospectively or imputed using appropriate proxies. Eligible respondents may not respond at all or may choose not to provide answers to certain questions. We will reduce the amount of missing data and non-response by using multiple modes of data collection (e.g., telephone, email, and in-person interviews) and leveraging collaborative relationships between HCS research staff and community stakeholders. In addition, we will have administrative data to support imputation for most participants. For example, we will have records of who attended coalition meetings and how long those meetings last even if a participant did not complete a coalition meeting survey. Finally, we will use model-based imputation (including multiple imputation when appropriate) and sensitivity analyses to account for missing data, sampling variability, and other sources of uncertainty (Briggs et al., 2003; Dunlap et al., 2018; Faria et al., 2014; Michalowsky et al., 2020). These methods will be conducted within the broader cost-effectiveness analysis described below.

2.3. Cost-effectiveness analysis

Our cost-effectiveness methodology follows best practices as described in the literature (Neumann et al., 2016). Following the design of the HCS study, we will calculate incremental effectiveness as the estimated difference in opioid overdose mortality in Wave 1 compared with Wave 2 communities in Year 2 of the CTH intervention. During this period of the CTH intervention, ORCCA EBPs will be fully implemented in Wave 1 communities, and no HCS interventions will have begun in Wave 2 communities.

By study design, Wave 2 communities do not have any CTH implementation costs during the phase where they are in the wait list condition. Wave 1 communities are assumed to have zero relevant costs before the beginning of the study. Therefore, the incremental cost of community implementation is the estimated total cost needed to implement CTH in Wave 1 communities in Year 1 and Year 2 of the CTH intervention.

The incremental cost of other resource utilization attributable to CTH is the estimated difference in costs between Wave 1 and Wave 2 communities occurring in Year 2 of the CTH intervention after controlling for potential confounders that were not accounted for in the randomization process (The HEALing Communities Study Consortium, 2020), such as communities' resource utilization in the year before Year 1 of the CTH intervention or pre-existing infrastructure that can be used to implement CTH EBPs. Such differences may influence which EBPs are adopted by each community and the resources needed to implement them. The HCS is systematically collecting data to characterize communities' pre-CTH assets and infrastructure and is tracking decisions around EBP selection EBPs (Knudsen et al., 2020). Additionally, information on, funding related to EBPs and infrastructure from federal, state, and community sources is being collected, as well as funding received directly from the HCS. All of these factors will be used to evaluate the extent to which selection or other biases were not eliminated through randomization. To the extent that these factors appear salient, we will construct analytic variables that we will include as controls in our cost models.

We will estimate the incremental cost-effectiveness ratios (ICERs) between Waves 1 and 2, defined as the ratio of incremental costs to the difference in opioid overdose deaths, and that represents the incremental cost per additional opioid overdose death averted. ICERs will be estimated for both the community and the societal perspectives. Outcomes may be influenced by factors not balanced by randomization. In addition to model adjustments described above related to costs, we will incorporate adjustments used for the primary and secondary outcomes analyses in our cost-effectiveness analyses (Slavova et al., 2020).

We will use Monte Carlo, nonparametric bootstrapping (e.g., Dunlap et al., 2019), or parametric methods (e.g., Murphy et al., 2019) to characterize joint parameter uncertainty around our cost and ICER estimates (e.g., adjusted standard errors, confidence intervals). The methods will account for missing data and measurement error when data are observed and will be used jointly with multiple imputation and other sensitivity analyses to provide a comprehensive set of cost and cost-effectiveness results with well-characterized uncertainty.

We will also consider alternative values of key parameters or assumptions (parameter uncertainty) in sensitivity analyses. These alternative analyses range in complexity from simply including "high" and "low" alternative value scenarios to sampling explicitly from specified probability distributions of possible ranges for cost and effectiveness.

To evaluate the cost-effectiveness results, we will assess how stakeholder willingness to pay (WTP) affects the results. Cost-effectiveness acceptability curves (CEACs) will be an important tool for exploring the probability that CTH is cost-effective compared with no CTH intervention over a range of stakeholder WTP values of cost per opioid overdose death avoided. CEACs incorporate the joint variability of the cost and outcome estimates and show the probability that an intervention is the cost-effective choice as a function of the policy maker's WTP over a range of values (e.g., $100,000 to $200,000 WTP per opioid overdose death avoided) (see Neumann et al. (2014) and Murphy et al. (2017) for QALY WTP examples).

3. Simulation modeling

The HCS HES will use simulation modeling to evaluate the short- and long-term health and economic impacts of the CTH intervention and to develop a policy tool for communities that want to implement CTH. Simulation modeling will be used to extend the cost-effectiveness analysis described above to alternative community scenarios and longer time horizons. Models will provide a "lifetime" time horizon and enable us to estimate the cost-effectiveness of the HCS intervention on a cost per QALY gained basis. The Second Panel (Neumann et al., 2016)

recommends using QALYs as an outcome measure in CEA, which are years of life saved adjusted by the quality of those years. QALYs are useful because they combine mortality and morbidity into a single metric, reflect societal preferences for the value assigned to each year of life, and can be used as a standard measure of health gains across diverse treatments and settings (Neumann and Cohen, 2018). Cost per QALY estimates will allow us to compare the economic value of HCS with other community-based interventions.

The HCS HES will benefit from simulation models that will be developed through a collaborative approach among modelers representing each research site and the data coordinating center. Several modeling approaches will be used, including agent-based modeling (ABM), microsimulation, system dynamics, and dynamic compartmental models (Neumann et al., 2016). Throughout the model building and estimation processes, modelers will share progress and compare key model outputs, enabling model cross-validation. Although models will be built independently, they will share parameterization approaches and be subject to the scrutiny of other modelers, thus improving the face validity and internal validity of each model (Eddy et al., 2012). Developing simulation models will also benefit from continuous engagement with community stakeholders, so modelers can ensure the most up-to-date inputs are used and that the outcomes are of greatest interest to decision makers.

All models will simulate the trajectory of opioid use disorder by modeling transition of people to different stages of opioid use including opioid misuse and OUD, remission, relapse, fatal and nonfatal overdoses, and/or death (Chen et al., 2019; McLellan et al., 2000). This structure enables EBPs adopted in each community to potentially alter individuals' trajectories, which will subsequently affect their lifetime costs, mortality, and quality of life.

Models will use two types of parameters, those that are context-specific to communities and those that can be applied more generally across communities—parameters that characterize details of OUD epidemiology and treatment seeking behaviors are context specific, while parameters about the pharmacologic efficacy of treatment and quality of life with OUD are generalizable. Context-specific parameters include population size, prevalence and incidence of opioid misuse, prevalence of OUD, opioid overdose deaths, other causes of death, MOUD admissions, and MOUD retention. General parameters include MOUD efficacy and the relative risk of death both during and immediately following MOUD treatment. Other general parameters are utility weights representing quality of life with OUD or opioid use. These inputs will be drawn from national or publicly available data sources (e.g., CDC) and published literature. We will account for parameter uncertainty as described in Section 2.3.

Key model outputs will include temporal trends in population health outcomes such as fatal and nonfatal opioid overdoses, number of individuals misusing opioids, number of individuals with OUD, number receiving and maintaining use of MOUD, and naloxone coverage. Additionally, models will estimate the long-term impact of EBPs on costs, opioid overdoses, life years gained, and QALYs. Although HCS will not examine the effectiveness of individual EBPs, the models could account for synergies among multiple practices to explore the relative impact of different intervention combinations beyond the short-term period of the EBP interventions implemented at the research sites. The models can thus inform optimal resource allocation at the community level to achieve a targeted reduction in opioid overdose deaths.

3.1. Opioid policy simulator

One of the goals of the HCS HES is to inform CTH implementation decisions by communities not participating in the HCS. We will develop the Opioid Policy Simulator which will be an interactive online translational tool for policy makers and non-HCS communities to use as they plan their approaches to reducing opioid overdoses. One of the HCS modeling teams has previously developed similar web-based tools for Hepatitis C infection (Chhatwal et al., 2018) and for COVID-19 (www.covid19sim.org). The inputs and outputs of simulation models will feed the simulator through a "metamodeling" approach (Ferreiro-Cabello et al., 2018), and the simulator will provide outcomes like the numbers of opioid overdose deaths, nonfatal overdoses, number of people with OUD, and cost-effectiveness of EBP interventions in different communities. It will also allow users to explore economic impact on budgets for specific payers, like Medicaid. Users will be able to use the simulator to assess the health and economic impact of opioid policy scenarios in other areas of the country impacted by the opioid crisis, allowing translation of HCS results to these communities.

4. Discussion

The HCS offers an unprecedented opportunity to conduct health economics research on solutions to the opioid crisis. HCS is the largest implementation science, addiction research study ever conducted in the United States. Implemented in 67 communities across four states, CTH combines a community-level approach with combinations of EBPs and communication campaigns to significantly reduce opioid-related overdose fatalities. The breadth and scale of CTH offers a rich environment from which to draw lessons learned for other communities combating the opioid crisis and presents a unique opportunity for health economics analyses. The HCS HES complements the HCS by providing critical estimates of the resources needed to implement CTH, its broader impact on societal resources, and its cost-effectiveness for avoiding overdose deaths. Simulation modeling will incorporate these results to characterize CTH's impact better, allowing for extrapolation of results to non-HCS communities to support planning and policy making around similar interventions. The models developed will evaluate combinations of different interventions and consider synergies across interventions in the continuum of OUD prevention, harm reduction, and treatment—an endeavor that no OUD simulation model has yet achieved (Barbosa et al., 2020; Nosyk, 2020).

The HCS is a complex and challenging intervention, and the HES has several limitations. First, implementing CTH relies on the efforts of numerous and disparate individuals and organizations within and outside CTH communities who will be engaged in a variety of different implementation activities. Collecting accurate and representative information about how individuals spend their time to implement CTH without causing excessive respondent burden is challenging. It requires flexible and tailored data collection instruments and strategies to make use of alternative data sources, including administrative data and literature-based estimates.

Second, defining measures of resource utilization changes associated with CTH is also challenging, especially for the societal perspective. For example, a key limitation of the economic study is that change in health care costs over the study period will be measured using primarily using data on Medicaid-enrolled individuals. This population represents a large portion of all individuals with an OUD diagnosis or who are receiving OUD treatment. (Orgera and Jennifer, 2019). However, our cost estimates, even after adjusting health care, may not be representative of the entire population targeted by the study. Furthermore, despite making adjustments for confounding community-level characteristics, our estimates may still suffer from selection bias or bias from unobserved or poorly measured characteristics.

Finally, we note the impact of the COVID-19 pandemic on the HES, which has disrupted Wave 1 communities implementing CTH. For example, the capacity of some community stakeholders to implement CTH early in Year 1 of the intervention was reduced to focus on the COVID-19 pandemic. Additionally, a possible disruption of the illicit opioid supply because of COVID-19 may have effects on opioid-related outcomes and opioid-related demands on health care and other resources in both Wave 1 and Wave 2 communities. Despite these challenges, communities are adapting how they are implementing CTH in ways that may provide useful models for other communities. For

example, MOUD have started being prescribed through telehealth. The HES is well-positioned (1) to learn lessons from COVID-19 by comparing implementation costs in Wave 1 and Wave 2 communities and (2) to account for the opioid-related impacts of the pandemic through simulation modeling.

In conclusion, the HCS HES includes economic evaluation and simulation modeling components that will provide valuable insights for both HCS and non-HCS communities. As policy makers and other stakeholders address the devastating effects of the U.S. opioid crisis, these data will show how community and societal resources can be deployed most effectively to reduce opioid overdose deaths.

Role of the funding source

This research was supported by the National Institutes of Health (United States) through the NIH HEAL Initiativeunder award numbers UM1DA049406 (Kentucky), UM1DA049412 (Massachusetts), UM1DA049415 (New York), UM1DA049417 (Ohio), and UM1DA049394 (RTI).

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or its NIH HEAL Initiative.

Contributors

All authors have contributed materially in developing the overall health economics study design. All authors also contributed to manuscript preparation, reviews, and substantial edits. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgements

We acknowledge members of the HCS Health Economics Workgroup who have provided ongoing feedback and other assistance for the study protocol, data collection approaches and planned analyses (Thomas Clark, Carter Roeber, Katie Marks, Drew Speer, Iván Montoya, Imaan Umar, Brenda Amuchi, Danielle Ryan, Kerry Keyes, Elwin Wu, Joseph Thompson, Erica Onuoha, John Bridges, Wilson Figueroa, Amy Knudsen, Steven Orme, Rasika Ramanan, Jackson Luckey, Colleen Watson, and Brent Gibbons). We also thank others across the HCS Consortium for overall project leadership, supporting the health economics study and thoughtful inputs to help the health economics study coordinate both scientifically and practically with this large and complex study.

IQVIA data are not reported in this paper, but IQVIA is mentioned as a data source; therefore, the manuscript was reviewed and approved by IQVIA.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2020.108336.

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