Next Steps in Designing for Diffusion of Pre-Exposure Prophylaxis
Demonstration Projects

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> What will it take to achieve what U.S. Secretary of State Hillary Rodham Clinton called, in a 2011 address, an 'AIDS-free generation'?. . . This goal requires an ambitious implementation-science agenda.[1]

One of the sharpest arrows in the implementation and dissemination quiver is the demonstration project. Many governments use demonstrations to study and to showcase interventions, from breastfeeding programs to wastewater treatment facilities to smart grid technologies. Yet demonstrations are of differing types, with varied objectives. Matching the type of pre-exposure prophylaxis (PrEP) demonstration to objectives is critical if delivery of PrEP and related HIV prevention care is to be established as feasible, adopted at nonstudy clinics, and implemented widely to positive effect.

Background

Demonstrations exist for one of two main reasons. A demonstration is either an experiment of a promising intervention, or a showcase of a proven intervention.[2] An *experimental demonstration* is a field test carried out for the purpose of assessing the external validity or practice feasibility of an intervention by varying the setting, participants, resource availability, implementation protocol, or the methods by which outcomes are measured. The purpose of an experimental demonstration is data collection and analysis to assess how best to deliver an intervention. Experimental demonstrations address the question, "Can this model work under something close to real-world conditions?" Some field experiments are designed so that staff can use data-based group decision processes (such as plan–do–study–act improvement cycles) to improve the fit between the intervention and the demonstration setting during the course of the study. Experimental demonstrations occur prior to determining whether an intervention should be actively disseminated. Experimental demonstrations help intervention developers and researchers reduce their own operational uncertainty—a necessary precursor to reducing subsequent potential adopters' operational uncertainty. Experimental demonstrations have the objectives of being conducted with modest visibility, characterized by quantitative control and evaluation, simulations of some aspects of the practice environment, and of a scale only as large as needed to derive the desired data. The posture of experimental demonstration management is one of healthy skepticism[2] or disinterestedness about specific methods for delivering an intervention.[3] Once this type of demonstration is completed, a second type of demonstration may be warranted.

An *exemplary demonstration* is a persuasive event intended to influence adoption decisions by being a part of a dissemination strategy, and thus increase the likelihood of diffusion to nonstudy sites. An exemplary demonstration is not conducted for the purpose of merely disseminating information; rather, the objective is to illustrate the delivery of an intervention in a convincing manner.[4,5] Exemplary demonstrations increase the likelihood of diffusion partly by making a costly, worrisome, and complex intervention more understandable through visibility of its processes and observability of its outcomes.

Exemplary demonstrations have the objectives of being highly visible, under sufficient control for credibility, in a fully operational setting, and at the fullest scale possible. The posture of exemplary demonstration–site personnel is optimistic assurance. The fact that some visitors to, or distant observers of, an exemplary demonstration will learn enough to decide against adopting the intervention as demonstrated is to be expected and is in itself a positive result: It is adoption of an intervention that will prove incompatible with a potential future setting that is to be avoided.[6,7]

Lack of clarity about the purpose of a demonstration is a frequent culprit in the nondiffusion of effective interventions.[8] A disconfirmed hypothesis that leads to a design improvement is a positive result in an experimental demonstration; in an exemplary demonstration, such an outcome is noise that will lead to perceptions of higher, not lower, uncertainty among potential adopters,

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thus increasing the number of decisions to not adopt the intervention.[9] In a study of the effect of composite experimental and exemplary demonstrations in the diffusion of evidence-based counseling programs, mixed-purpose demonstrations led to heightened interest in the innovations but not adoption.[10]

Diffusion is facilitated by exemplary demonstrations that apply what is known about the timing and framing of introducing innovations, positive portrayals based on innovation attributes, opinion leadership, and implementation support.[11] Those that present cost-effectiveness data to visitors and observers and answer their questions in the near term also speed diffusion.[5] An exemplary demonstration may follow an experimental demonstration at the same site or may be conducted at a different site.

Distinctions can be made among experimental demonstrations just as they can among exemplary demonstrations. The current paper identifies four classes of demonstrations, two experimental and two exemplary, with relevance for PrEP (Table 1). An open-label study is a clinical trial without researcher or participant blinding, with participants randomized to different conditions or without a control or comparison condition, and with all participants knowingly receiving the same intervention.

Open-label studies are typically used to observe longer-term adverse effects than those that can usually be observed in an RCT; continued efficacy of a drug; and instances in which ethical considerations make a no-treatment condition undesirable. An implementation pilot study is used for assessing practical feasibility of intervention delivery in nonresearch clinics, without restrictive inclusion/exclusion criteria, guided by the development and refinement of practice protocols to assist (and improve) implementation decisions. Study objectives usually concern acceptability by the clinic, compatibility with workflow, and the effects on outcomes of variations in practice.

Exemplary demonstrations can have a single sponsor, which may be a federal agency, or may be a product of a partnership that reflects shared objectives among the private sector, the nonprofit sector, and a government agency to share the costs of conducting the demonstration. Single-sponsor demonstrations seek to convince observers of the worth and applicability of an intervention, aid observers' perception that uncertainties have been adequately resolved, and generate "demand pull" among potential adopters. They also generate political pressure through the efforts of advocates, and highlight the importance of institutional barriers that must be changed for the intervention to be widely deployed.[2]

The designers of integrated demonstrations pursue these same objectives by more directly "building the business case" through private-sector investment and cost analysis, and by confronting and resolving associated issues of licensing, liability and insurance, and regulation. This class of demonstrations can be further integrated in terms of showcasing multiple interdependent interven-

Table 1. Demonstration project typology

	Experimental types		Exemplary types	
	Open-label studies	**Implementation pilot studies**	**Single-sponsor demonstrations**	**Integrated demonstrations**
Type-specific questions	Acceptability (patients); medication adherence; longer-term safety	System acceptability; retention in prevention care; sustainability (cost, reimbursement); practice variation effects on outcomes	Interest, adoption, adaptation, implementation, sustained use	Partnership, coordination, interest, adoption, adaptation, implementation, sustained use
Setting(s)	Research clinics	Usual clinical sites	Usual clinical sites	Public health and clinical sites
Population(s)	Clinical trial participants (or similar)	Broad population that may benefit	Potential adopters	Potential adopters
Incentives	Money for time and effort	Clinical services only	Nonmonetary	Nonmonetary
Protocol	Strict research protocol	Practice guidelines	Dissemination guidelines, implementation guidelines	Dissemination guidelines, implementation guidelines
Provider(s)	Research staff	Community providers	Community providers	Community providers
Funding	Research funds	Insurance (public, private, or self)	Innovation sponsor	Combined sponsorship

tions such as those that exist for PrEP from the suite of combination prevention approaches and tools. So the demonstration is integrated in what it showcases and in its sponsorship.

Federal Experience with Demonstrations

Nonprofit organizations and commercial businesses rely heavily on demonstrations. Federal governments, especially, have impressive histories of support for the demonstration of new technologies, programs, and practices. Part of the reason for this support is that what is demonstrated often represents a radical new way to conceive of providing a service or product, requiring risks too large for single companies or nonprofits to assume.

The U.S. has been supporting demonstrations of new technologies for 170 years since the U.S. Congress appropriated $30,000 for Samuel Morse to demonstrate his American Telegraph System in 1843. This successful demonstration led directly to the diffusion of telegraph service in the U.S. Demonstrations can provide compelling evidence to observers that a technology, program, or practice should be adopted. This effect of demonstrations in stimulating diffusion is based in visualization and tangible observable evidence of intervention effectiveness. Visitors often come onsite to see for themselves. The effect of seeing for one's self also has the effect, in the case of successful demonstration, of reducing perceived differences between innovation sources and potential adopters.[9]

Federal agencies in the U.S. rely on demonstrations to both assess and diffuse innovations. It has been estimated that up to 10% of the government's research and development budget is spent in demonstrations.[4] European nations and organizational members of international agencies have sponsored thousands of demonstrations of innovations.[8] The U.S. Department of Agriculture (USDA), through its Extension Service, state experimental stations, and state land-grant colleges, made the demonstration of agricultural innovations a central part of its highly successful diffusion system.

This tradition of demonstrations continues today. Demonstrations have been used during the past 40 years to diffuse energy and environmental innovations. The U.S. Atomic Energy Commission Power Reactor Demonstration Program of the 1950s is credited with having speeded commercial adoption of power reactor technology. The U.S. Energy Research and Development Administration demonstrated synthetic fuels. In the 1960s and 1970s, the Environmental Protection Agency demonstrated mechanized refuse collection (garbage trucks with mechanical arms); refuse burning; recycling and resource recovery; and poultry waste–processing technologies.

The Urban Mass Transportation Administration has sponsored hundreds of demonstrations of intelligent highways, car pooling, kiss-and-ride drop-off locations, pedestrian malls, and other innovations.[5,8] Demonstrations are a frequent means for communicating the advantages of educational innovations and how innovations operate at scale so that they may be diffused more readily from school district to school district.[12] The CDC has a rich tradition of supporting demonstrations of large-scale interventions designed to improve population health at the community level.[13,14]

From Experimental to Exemplary?

Recent efficacy studies of PrEP[15] along with U.S. Food and Drug Administration approval of Truvada® to reduce the risk of sexual acquisition of HIV infection in uninfected people who are at high risk of HIV exposure[16] suggest that a carefully designed implementation pilot study may be warranted to explore the clinical, behavioral, healthcare delivery, and public health questions surrounding its introduction. An experimental demonstration could, for example, be designed to address real questions from patients, providers, and policymakers; assess participation and representativeness; assess costs; and allow for and study adaptations in practice without relying on the strict inclusion/exclusion criteria required for clinical trials.[17]

For a PrEP experimental demonstration to be as realistic as possible, clinics selected should already serve individuals at high risk of acquiring HIV infection, whether they are high-risk heterosexuals or men who have sex with men; exhibit capacity and motivation to implement PrEP; reflect variance in geography; have HIV/STD services available onsite (such as Federally Qualified Health Centers or similar types of clinics); use an electronic medical record system for ease of data collection and to ensure automated prompts and reminders can be sent to clinicians and patients; and not be involved in other PrEP studies. Selected experimental demonstration sites should have the capability and willingness to involve staff in PrEP delivery improvement teams, engage in outreach to HIV-uninfected people at high risk for HIV acquisition, screen for clinical and behavioral indications for PrEP use, bring in the patient for periodic repeat HIV testing, and engage the patient in counseling to reinforce risk-reduction practices and adherence to daily medication.[18]

If the results of experimental demonstrations suggest that specific clinical approaches to PrEP should be actively disseminated, then planning an integrated demonstration may be particularly warranted. Convening a discussion with commercial firms (such as Gilead Sciences, Inc., Truvada's manufacturer); regulatory agency repre-

sentatives; insurers; and public health officials could result in the sort of exemplary demonstration that would prove informative and convincing.

The decision regarding which sites should be selected for experimental demonstrations is important because the social identity of the host organization can affect the perception of visitors to the site (or other observers) in their estimation of how likely the intervention is to be implemented. Along with the site-selection criteria mentioned above, the reputation among peer and near-peer clinics of each proposed clinic site should be considered. Also, a regional approach to selecting a set of clinics could be an objective because observers often are actively looking for ways that their organization and clients differ from, or are similar to, what they are observing. Planners can anticipate and counter the not-invented-here response among demonstration observers by selecting clinic sites so that observers can evaluate demonstration results for a clinic that they perceive to be more or less like their own, perhaps in the same city, serving the same demographic, with the same lack of resources.

Observers of PrEP exemplary demonstrations could include public interest groups, clinical interest groups regulators, investors, elected officials and government staff, and centrally the potential adopters of PrEP: clinical leaders and clinician managers. Because any demonstration has a finite carrying capacity, select personal outreach should be considered to those potential adopters who are known as credible among their peers and near-peers: informal opinion leaders. Some credible individuals have extraordinary reach into diverse policy communities and would make excellent candidates for visitors to a PrEP exemplary demonstration.[19] Evidence-based messages about the PrEP implementation before them, including talking points in which staff are trained on the basis of attributes that are positively associated with adoption, will facilitate interest among visitors.[11]

Exemplary demonstrations can be collaborative learning and refining experiences for clinic staff and researchers. Integrated demonstrations, especially if they showcase multiple complementary interventions such as primary care assessment of patients, Truvada prescription and instruction, safer-sex education, care coordination, repeat HIV testing, and behavioral health counseling can be conceptualized as a set of tasks, for each of which specific delivery and coordination procedures can be of considerable interest to the visitor. Each task represents a component of a set of activities organized to accomplish a goal related to PrEP (reduced HIV acquisition), the coordination of which has the potential to be complex. One exemplary demonstration studied by one of the present authors (JWD) consisted of 32 tasks involving more than 100 staff members. To the extent that demonstration-site staff or researchers use an exemplary demonstration as an opportunity to learn about intervention redesign, the function of the demonstration becomes conjoined with that of experimental demonstration.

Finally, exemplary demonstrations, like experimental demonstrations, are objects of study as well as practice. The extent to which PrEP is tried, adopted, implemented at nonstudy sites, and sustained in clinics for the benefit of individuals at high risk of HIV acquisition are diffusion outcomes that can be modeled as a result of demonstration intervention in an overall dissemination strategy.

Conclusion

Pre-exposure prophylaxis, a biomedical intervention with potential to be highly effective if well implemented and used, appears well suited to sequential demonstration, first for experimental purposes with the objective of assessment of feasible delivery methods, and second for exemplary purposes with the objective of promoting its effective implementation. It is sometimes practical that the same clinical sites can serve both purposes, although with somewhat divergent clinic-selection criteria, it is wise to disentangle experimental from exemplary demonstration. Exemplary demonstrations, as one possible component of a dissemination strategy to accelerate and broaden diffusion, enable observers to be convinced, in the near term, by seeing and asking questions of staff currently involved in implementation, and to gain immediate feedback.

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