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Title: Can We Build an Efficient Response to the Prescription Drug Abuse Epidemic? Assessing the Cost Effectiveness of Universal Prevention in the PROSPER Trial

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Abstract: Purpose: Prescription drug abuse has reached epidemic proportions. Nonmedical prescription opioid use carries increasingly high costs. Despite the need to cultivate efforts that are both effective and fiscally responsible, the cost-effectiveness of universal evidence-based-preventive-interventions (EBPIs) is rarely evaluated. This study explores the performance of these programs to reduce nonmedical prescription opioid use.

Methods: Sixth graders from twenty-eight rural public school districts in Iowa and Pennsylvania were blocked by size and geographic location and then randomly assigned to experimental or control conditions. Within the intervention communities, prevention teams selected a universal family and school program from a menu of EBPIs. All families were offered a family-based program in the 6th grade and received one of three school-based programs in 7th-grade. The effectiveness and cost-effectiveness of each school program by itself and with an additional family-based program was assessed using propensity and marginal structural models.

Results: This work demonstrates that universal school-based EBPIs can efficiently reduce nonmedical prescription opioid use. Further, findings illustrate that family-based programs may be used to enhance the cost-effectiveness of school-based programs.

Conclusions: Universal EBPIs can effectively and efficiently reduce nonmedical prescription opioid use should be further considered when developing comprehensive responses to this growing national crisis.

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4 *Can We Build an Efficient Response to the Prescription Drug Abuse Epidemic?*
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6 *Assessing the Cost Effectiveness of Universal Prevention in the PROSPER Trial*
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4 **Abstract**

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8 opioid use carries increasingly high costs. Despite the need to cultivate efforts that are both
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10 effective and fiscally responsible, the cost-effectiveness of universal evidence-based-preventive-
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*Can We Build an Efficient Response to the Prescription Drug Abuse Epidemic?
Assessing the Cost-Effectiveness of Universal Prevention in the PROSPER Trial*

Prescription drug abuse has reached epidemic proportions in the United States with youth populations being especially vulnerable to abuse and addiction (CDC, 2011; Fischer et al., 2008; Havens, 2011; Hernandez and Nelson, 2010; Manchikanti and Singh, 2008; Maxwell, 2011; ONDCP, 2011;). At the center of this growing crisis are prescription opioids, with over 12 million Americans having used this pharmaceutical class for nonmedical purposes. Adolescent populations are particularly vulnerable to opioid misuse and abuse, with early initiation increasing the likelihood of future addiction (Compton and Volkow, 2006; McCabe, 2012, 2011, 2009; Meier, 2012). In turn, these nonmedical users are estimated to cost society over \$53 billion each year through their greater burden on health and service systems as well as increased rates of disability (Birnbaum et al., 2011; Coben et al., 2010; Hansen et al., 2011a; Johnston et al., 2010; SAMHSA, 2009).

The rise in nonmedical prescription opioid use poses a major threat to public health and many policy makers are seeking to craft practical responses (ONDCP, 2011). Unfortunately, devising cost-effective initiatives that do not compromise pain management practices remains difficult (FDA, 2013; Fischer et al., 2008; Katz et al., 2007). Despite development of approaches for reducing misusers' access to prescription opioids (e.g., prescription-monitoring-systems, interdiction efforts), supply side methods are often resource intensive and may be difficult to effectively deploy during times of budgetary uncertainty. Instead policymakers may wish to engage more efficient solutions (Spoth, 2011a). For instance, demand reduction approaches that prevent nonmedical use, especially in at-risk populations, may offer a more fiscally responsible option (Catalano, 2009; Currie, 2005; O'Connell et al., 2009; Spoth, 2011b).

One such approach is the use of universal school and family evidence-based-preventive-interventions (EBPIs). Universal prevention programs¹ target a whole population group (e.g., school) that has not been identified based upon individual risk (e.g., prenatal care, childhood immunization; (Greenberg et al., 2001). For instance, universal school programs are offered to all students in a school and universal family programs can be offered to all families in community with no prior screening. These programs differ from other demand reduction

¹ *Not to be confused with universal precautions taken by prescribers to reduce the risk of misuse among patients (Gourlay and Heit, 2009)*

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4 approaches (e.g., public education and awareness campaigns) through their focus on reducing
5 substance abuse risk (pro-abuse norms and expectations of use) and cultivating protective factors
6 (refusal skills, social bonding, parental monitoring; (Hawkins et al., 1992; Kumpfer and
7 Alvarado, 2003). Universal EBPIs are increasingly delivered within the context of formal
8 prevention delivery and support systems that facilitate implementation and sustainability of
9 prevention efforts (e.g., *PROSPER*, *Weed & Seed*, *Communities-that-Care*, *SPF-SIG*, *Getting-to-*
10 *Outcomes*; (Crowley et al., 2012; Hawkins, 1992, 2009; Spoth et al., 2004; Wandersman, 2000).
11 Large demonstration trials, including the PROSPER study, have illustrated that EBPIs, delivered
12 within these systems, represent a promising strategy for reducing nonmedical prescription opioid
13 use (Aos et al., 2011, 2004; Guyll et al., 2011; Spoth et al., 2007a, Under Review; Spoth, 2006),
14 but relatively little work has sought to evaluate these programs' capacity to efficiently reduce
15 nonmedical prescription opioid use in everyday contexts (Spoth et al., 2008). This lack of
16 evaluation has contributed to universal EBPIs being largely overlooked and underutilized in
17 recent federal and state responses.
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30 Limited work in this area has in part resulted from data limitations and methodological
31 uncertainty around how to model the complex selection effects that lead to individuals receiving
32 preventive interventions in school and family health service settings. In order to better
33 understand the capacity of universal prevention efforts to reduce nonmedical prescription opioid
34 use, we demonstrate a methodological approach to evaluate the cost-effectiveness of receiving
35 multiple preventive interventions within different service settings. Specifically, through the use
36 of propensity and marginal structural models we are able to first model who receives different
37 programs when they are delivered in actual service contexts and then use these models to assess
38 the incremental cost-effectiveness of programs. This differs from previous work that has
39 assessed universal prevention largely within tightly controlled research trials that may
40 overestimate intervention impact when programs are translated to non-research contexts. We
41 first evaluate the cost-effectiveness of three substance abuse school-based EBPIs to prevent
42 nonmedical prescription opioid use (Life Skills Training, All Stars & Project Alert) delivered
43 within the PROSPER delivery and support system. Next, the impact of a combined school and
44 family-based programming approach is assessed for each of the three school programs with a
45 family-based EBPI (SFP:10-14). This work builds on current understanding of universal
46 prevention programs' effectiveness and provides insight into their cost-effectiveness. Through
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these analyses we gauge the real-world performance of universal programs in order to identify cost-effective approaches for reducing this growing epidemic.

Methods

In order to evaluate the cost-effectiveness of the four universal EBPIs in actual service settings, propensity and marginal structural models were fitted within a cost-effectiveness analysis of the PROSPER dissemination trial.

Sample

The National Institute of Health funded PROSPER dissemination trial included 14 communities in Iowa and 14 communities in Pennsylvania based upon four criteria that included (1) school district enrollment between 1,301 and 5,200 students, (2) at least 15% of families eligible for reduced cost lunch, (3) maximum of 50% of the adult population employed at or attending a college or university, and (4) the community could not be involved in other university-affiliated, youth-focused prevention initiatives. Communities were matched by geographic location and size; each pair of communities was randomized into intervention and control conditions by the principal investigators (Spoth et al., 2007b, 2004). Approximately half the sample comprised the control condition (N=5,292; Figure 1). Within the intervention communities, local prevention teams led by local cooperative extension agents and school officials selected a universal family and school program from a menu of EBPIs (Spoth et al., 2004). All families in intervention communities were offered the Strengthening Families 10-14 program (SFP:10-14) in the 6th grade, but not all families enrolled (N=827). In addition, all youth in the intervention communities (N=5,026) received one of three school-based substance abuse programs in the 7th grade (All Stars (N=1,936), Life Skills Training (N=1,166) and Project Alert (N=1,924). Thus while the PROSPER participants were randomized to either intervention or control groups, the type of school intervention they received and whether they attended the family program was not randomized. Additional information about the different EBPIs may be found in Appendix 1. Program adherence was high for both school and family programs ($M = 90\%$; see (Spoth et al., 2011). The participating universities' IRBs approved the study procedures before recruitment began.

Measurement

Estimates of Program Cost. The costs of the evidence-based prevention programs delivered within the PROSPER dissemination trial were estimated in an earlier prospective five-

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4 year cost analysis (Crowley et al., 2012). Opportunity costs were estimated from budgetary,
5 sustainability, and volunteer-time data that tracked both expenditures from the parent grant and
6 inputs from any outside sources. The cost to provide a school program to a single student was
7 between \$9-\$27 and the average cost to provide the family program to a single family was
8 between \$311-\$405. These costs included expenditures on curriculum and program supplies,
9 facilitator time, family attendance incentives and volunteer/in-kind donation for programming.

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13 **Nonmedical Prescription Opioid Use.** To evaluate youth nonmedical prescription
14 opioid use, each participant was asked whether they had ever used prescription opioids for
15 nonmedical purposes at the 6th grade pre-test (2002-2010) and at the end of each year through
16 12th grade [*Have you ever used Vicodin®, Codeine, Percocet or OxyContin® not prescribed by a*
17 *doctor?*].

24 **Analytic Approach**

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26 As described above, PROPSER participants were randomized at the community level to
27 treatment groups. However, which school-based EBPI they received was chosen by each
28 community's team and families chose whether to attend the evening family program. Thus, in
29 order to estimate the benefits of receiving the different school programs as well as the benefits of
30 receiving the school and family programs together, a multi-step analytic framework was
31 employed. This included (1) estimation of participants' propensity to receive different programs,
32 (2) fitting marginal structural models to estimate the impact of receiving different programs on
33 ever using prescription opioids for non-medical purposes, (3) calculation of incremental cost-
34 effectiveness ratios, and (4) threshold analyses to assess whether a program represents an
35 efficient societal investment.

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39 *Propensity & Marginal Structural Models.* Propensity and marginal structural models are
40 well-established analytic tools used to improve causal inference when using observational data
41 (Robins et al., 2000; Rosenbaum and Rubin, 1983). Propensity models were employed here to
42 estimate the probability that an individual will receive each of the programs based upon a variety
43 of prespecified covariates (See Appendix 1). Within this evaluation, we estimated individuals'
44 probabilities of receiving seven possible outcomes (i.e., participants' propensity to receive either
45 no program, one of the three school programs, or one of the three school programs and the
46 family program). These probabilities were then transformed into inverse probability weights—
47 which may be used similarly to survey weights—to balance the different possible forms of
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4 treatment receipt on the confounders included in the propensity model. These weights were used
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6 to adjust marginal structural models, to estimate the effectiveness of the programs to reduce
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8 nonmedical prescription opioid use. PROC GLIMMIX was implemented to fit multi-level
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10 logistic models that accounted for the nested structure of the trial (i.e., participant nested within
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12 school, (Littell, 2006) Further description of the covariates that were included in the propensity
13
14 models and how the propensity and marginal structural models were implemented may be
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16 accessed in Appendix 1 & 2.

17 *Incremental Cost-Effectiveness Analysis.* Next, the incremental cost-effectiveness ratios
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19 (ICERs) for different levels of program receipt were estimated (Figure 1). The numerator of an
20
21 ICER is the difference in costs for treatment outcomes (e.g., school program versus control). The
22
23 denominator of the ICER is the difference in the average effect sizes of the two interventions.
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25 ICERs were calculated for each program combination that significantly reduced nonmedical use
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27 compared to the control condition (at the $p \leq .05$ level). Statistical bootstrap techniques were
28
29 employed to construct 95% confidence intervals around each ICER (using 1000 replications;
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31 (Briggs et al., 1997)

32 *Threshold Analysis.* Each ICER was considered relative to the societal cost of allowing
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34 youth to engage in nonmedical prescription opioid use (i.e., Willingness-to-Pay). Recent
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36 analyses have placed the cost of nonmedical prescription opioid use at between \$53.2 and \$55.7
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38 billion annually. An estimated 12.5 million individuals reported using prescription opioids for
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40 non-medical purposes (Birnbaum et al., 2011; Hansen et al., 2011b). This translates into an
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42 approximate average societal cost of \$4,132 per nonmedical opioid user per year. The average
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44 course of nonmedical use for this age group (late adolescence and early adulthood) is 2.17 years
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46 (Catalano et al., 2011). Based upon this previous work, it can be estimated that youth who
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48 engage in nonmedical prescription opioid use cost society approximately \$8,966 per year. When
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50 discounted across the six years of program follow-up within the PROSPER trial, at a standard
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52 rate of 3%, this figure rounds to \$7,500 (Russell et al., 1996). This estimate serves as the basis
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54 for a Willingness-to-Pay (WTP) threshold, where allocating less than \$7,500 (i.e., the estimated
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56 societal cost of an adolescent or young adult nonmedical opioid user) to preventing a single case
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58 of nonmedical use is an economically efficient decision. In other words, if the 95% confidence
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60 interval of this ICER falls below this societal WTP, one could make a case that it is more
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4 efficient to allocate the resources toward prevention services versus doing nothing and allowing
5 the case of nonmedical opioid use to take its course.
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7 8 **Results**

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10 Here we consider the results of the effectiveness, cost-effectiveness, and threshold
11 analyses in order to ascertain the impact and efficiency of the three school programs with and
12 without the family program compared to those youth in the control group. As presented in Table
13 1, there is increasing lifetime use of prescription opioids across adolescence with over 25% of
14 seniors ever having used a prescription opioid that was not prescribed by a doctor.
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18 **Effectiveness Analyses.** The effectiveness of the different PROSPER program
19 combinations were evaluated to assess the impact of the school and family program, compared to
20 the control condition (Table 2; incremental effect). Receipt of the Life Skills Training Program
21 led to a significantly reduced probability of youth having ever used prescription opioids for
22 nonmedical purposes by grade 12 compared to the control condition (Control v. Life Skills
23 Alone: *3.9%-4.9% reduction*). No significant differences were observed between the All Stars
24 and Project Alert Programs compared to the control condition. Receipt of the Life Skills and
25 SFP:10-14 programs together as well as receipt of the All Stars and SFP:10-14 programs
26 together revealed a significant difference from the control condition (Control v. Life Skills &
27 SFP:10-14 Combined: *5.8%-10.5% reduction*; Control v. All Stars & SFP:10-14 Combined;
28 *6.8%-8.5% reduction*). Life Skills Training in conjunction with SFP:10-14 was the most
29 effective in reducing nonmedical prescription opioid use (Figure 2).
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41 **Cost-Effectiveness Analysis.** Table 2 provides ICERs (i.e., the difference of the average
42 of the predicted probabilities for the treatment and comparison groups) and their standard errors.
43 The Life Skills Training program alone compared to the control group had the lowest ICER and
44 thus is the program option with the greatest relative productive efficiency (ICER = \$613). One
45 may interpret this as a \$613 cost (95% CI: \$548-693) to prevent one youth from misusing
46 prescription opioids before 12th grade who would otherwise have engaged in nonmedical use if
47 they had not received the program.
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53 **Threshold Analysis.** The Life Skills Training program was the only school program that
54 when delivered alone significantly reduced nonmedical use compared to the control group. Thus,
55 the Life Skills Training program alone would be considered a cost-effective approach for
56 reducing nonmedical prescription opioid use. Further, when compared to the control group,
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4 individuals who received SFP:10-14 as well as either All Stars or Life Skills Training were both
5 below the WTP threshold. Thus both Life Skills and All Stars when delivered with SFP:10-14
6 significantly reduce nonmedical use and would be cost-effective allocation of societal resources.
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8 When compared to each other, where the Life Skills and SFP:10-14 combination has a lower
9 ICER than the All Stars and SFP:10-14 combination, we can infer that the most efficient
10 allocation of societal money would be to invest in the combined delivery of the Life Skills and
11 SFP:10-14 programs.
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17 **Discussion**

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19 Policy-makers and community leaders are actively searching for efficient responses to the
20 growing prescription drug epidemic (FDA, 2013; Maxwell, 2011; ONDCP, 2011). In particular,
21 due to prescription opioids' growing popularity among adolescents and young adults, it is vital
22 that any coordinated strategy meets the needs of this vulnerable population. Without an effective
23 approach for curbing nonmedical use, Federal agencies are being forced to restrict access to
24 prescription opioids –at the cost of greater burden on suffering patients (Volkow, 2011). The
25 present study builds on earlier reports universal EBPIs implemented effectiveness and
26 demonstrates that universal school-based EBPIs are capable of reducing nonmedical prescription
27 opioid use by youth in a cost-effective manner and may supplement costly approaches to monitor
28 and restrict access (Spath et al., 2008; Spoth et al., 2008). Further, this evaluation reveals the
29 potential of family-based EBPIs during early adolescence to enhance the efficiency of school-
30 based programs. Thus, by employing propensity and marginal structural models we are able to
31 leverage the unique data within the PROSPER trial to compare the impact of the different school
32 programs and family programs.
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44 In light of these findings, decision makers seeking to craft comprehensive responses to
45 prescription drug abuse may wish to consider the potential value of broader evidence-based drug
46 use prevention efforts that nurture healthy cognitions and behaviors by parents and youth. In
47 particular, current estimates illustrate that nonmedical use is continuing to rise despite early
48 efforts to stem the tide of abuse and now may be time to engage new options (ONDCP, 2011).
49 This approach may reduce demand for tertiary approaches which while cost-effective may garner
50 less public support (e.g., soboxone and methadone maintenance; Polsky et al., 2010).
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57 By employing the analytic approach described above we can better understand universal
58 prevention's cost-effectiveness, and these specific analyses reveal the value of intervening across
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4 ecological settings when targeting youth populations. Specifically, programs operating in school
5 and family settings may be crucial to successful efforts. These results also emphasize that, like
6 medical treatments, not all evidence-based programs are equivalent and that interventions that
7 have met accepted standards of evidence (e.g., Blueprints) may not be cost-effective. Lastly, this
8 work illustrates that different elements of a multifaceted response are not simply additive and
9 may in fact interact in important ways. For instance, when the Life Skills Training and All Stars
10 programs are delivered with the SFP:10-14 program their performance is enhanced. This is not
11 true for the Project Alert program, which was not significantly better or worse at preventing
12 nonmedical use when delivered with the SFP:10-14 program. Such unique interactions may also
13 extend to efforts that combine prevention with medical treatment, interdiction and enforcement.
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22 This evaluation sought to understand the cost-effectiveness of universal EBPIs
23 specifically on preventing prescription opioid abuse. This is likely a dramatic underestimate of
24 the total societal value from universal programs that are known to not only prevent other forms
25 of substance abuse (e.g., alcohol, tobacco, methamphetamines; Guyll et al., 2011; Spoth et al.,
26 2008b) but a variety of delinquent behaviors linked to long-term criminality and increased use of
27 social service systems (Aos et al., 2011). Nevertheless, compared to approaches that aim to
28 reduce nonmedical use that is already occurring (e.g., treatment), a prevention-oriented approach
29 to nonmedical use may be especially well-suited for society's current needs. For instance, opioid
30 addiction is generally considered a chronic illness and requires costly treatments that quickly
31 overburden community service systems (McLellan, 2000). Consequently, even small reductions
32 in those ever requiring treatment can save substantial public monies. Alternately, because of the
33 important role of prescription opioids in pain management, interdiction and enforcement efforts
34 may harm or stigmatize those with legitimate medical need. Universal prevention efforts that
35 serve entire populations, targeting risk and protective factors for nonmedical use, can offer
36 society a means of protecting youth populations from nonmedical use while allowing those who
37 are suffering access to the best possible therapies.
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51 **Limitations**

52 A substantial body of literature has illustrated that—across settings—adequate capacity is
53 essential for high-quality implementation of evidence-based programs and practices (e.g.,
54 hospital, school, clinical). It is increasingly advised that large-scale delivery of such efforts not
55 be attempted without formal capacity building (Samet, 2001; Spoth et al., 2004; Wandersman,
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2000). In particular, delivery of universal EBPIs without such support can lead to diminished impact and lower levels of program efficiency (Spoth et al., 2004). In response, substance abuse researchers working with youth populations have developed multiple support systems that can effectively cultivate and maintain such capacity (Dunworth et al., 1999; Hawkins, 1992; Spoth et al., 2004). To maximize the generalizability of these estimates, this study considers program impact when delivered within such a system (i.e., PROSPER; (Spoth et al., 2004). Thus these estimates are not applicable to attempts to deliver universal EBPIs without such support systems as both the costs and effectiveness are likely to differ.

A second limitation of this work pertains to the Willingness-to-Pay threshold based on recent cost-of-illness estimates of prescription opioid nonmedical use. These estimates consider the health and productivity outcomes of individuals misusing prescription opioids, but fail to capture many growing downstream costs (e.g., malpractice litigation, interdiction efforts). Additionally, as little contingent valuation work has sought to estimate Quality Adjusted Life Years (QALYs) for opioid misuse and none have estimated QALYs of nonmedical prescription opioid use within youth populations (Connock et al., 2007; Schackman et al., 2012). Consequently, these estimates most likely undervalue the total societal costs of nonmedical prescription opioid use. This in turn may have resulted in an overly conservative Willingness-to-Pay threshold. This lower threshold is unlikely to have influenced the inferences drawn from this study, as all programming options that significantly reduced nonmedical use were represented by ICERs well below the threshold. Thus this threshold should be updated as revised cost-of-illness estimates become available.

Lastly, it is possible that the control communities also had access to the programs implemented by the intervention communities. This may have led to potentially lower program effectiveness than observed within this evaluation and thus estimates of cost-effectiveness are likely conservative. Further research is needed to explore the cost-effectiveness of combining other substance abuse prevention programs, including those outside family and school settings.

Conclusion

With this work we seek to draw attention to the potential value of universal school- and family-based EBPIs as part of an efficient response to the growing prescription drug epidemic. Given the rapid changes in health care policy and the opportunities provided for prevention and health promotion services in The Affordable Care Act, the use of community-based prevention

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4 services will expand and the evidence here indicates that if effective programs are used it can
5 significantly reduce public and private cost (Koh and Sebelius, 2010). It is vital that future
6 research evaluate the effectiveness and cost-effectiveness of these programs and policies in
7 various US communities in order to truly craft the most efficient response.
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Figure 1

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Figure 1: Study Participation Summary

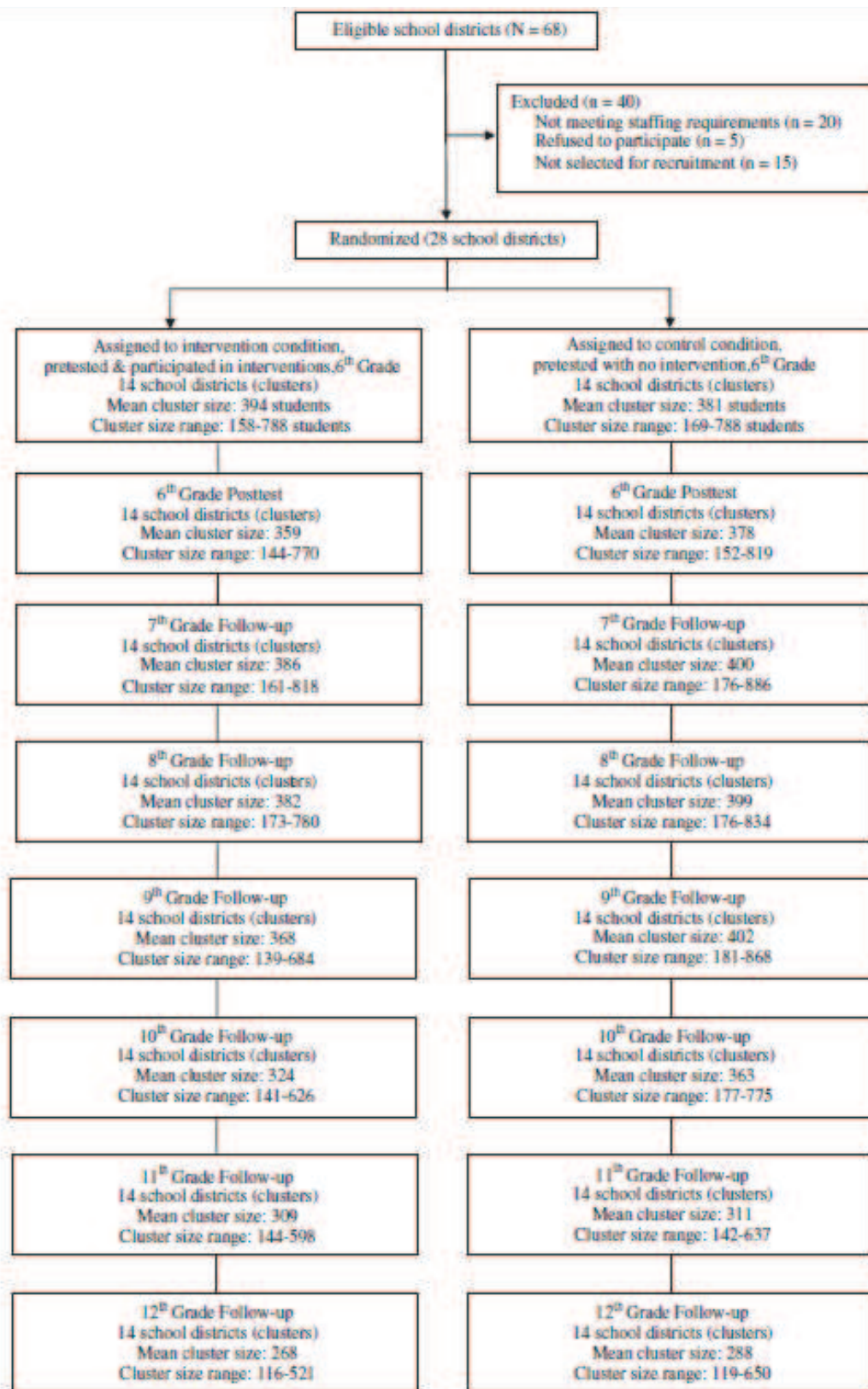


Figure 2: Decision Tree for Cost-Effectiveness Analysis

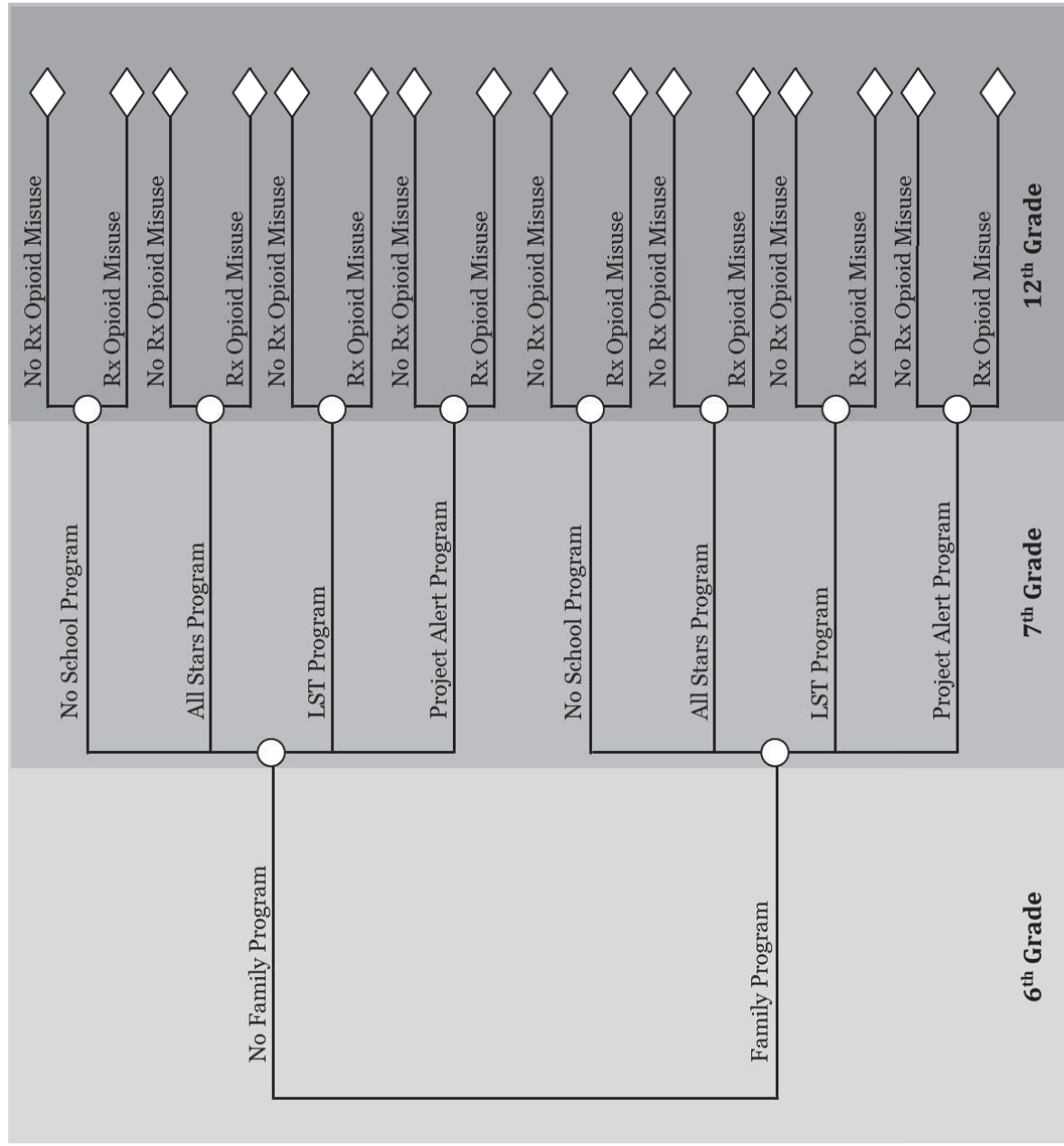
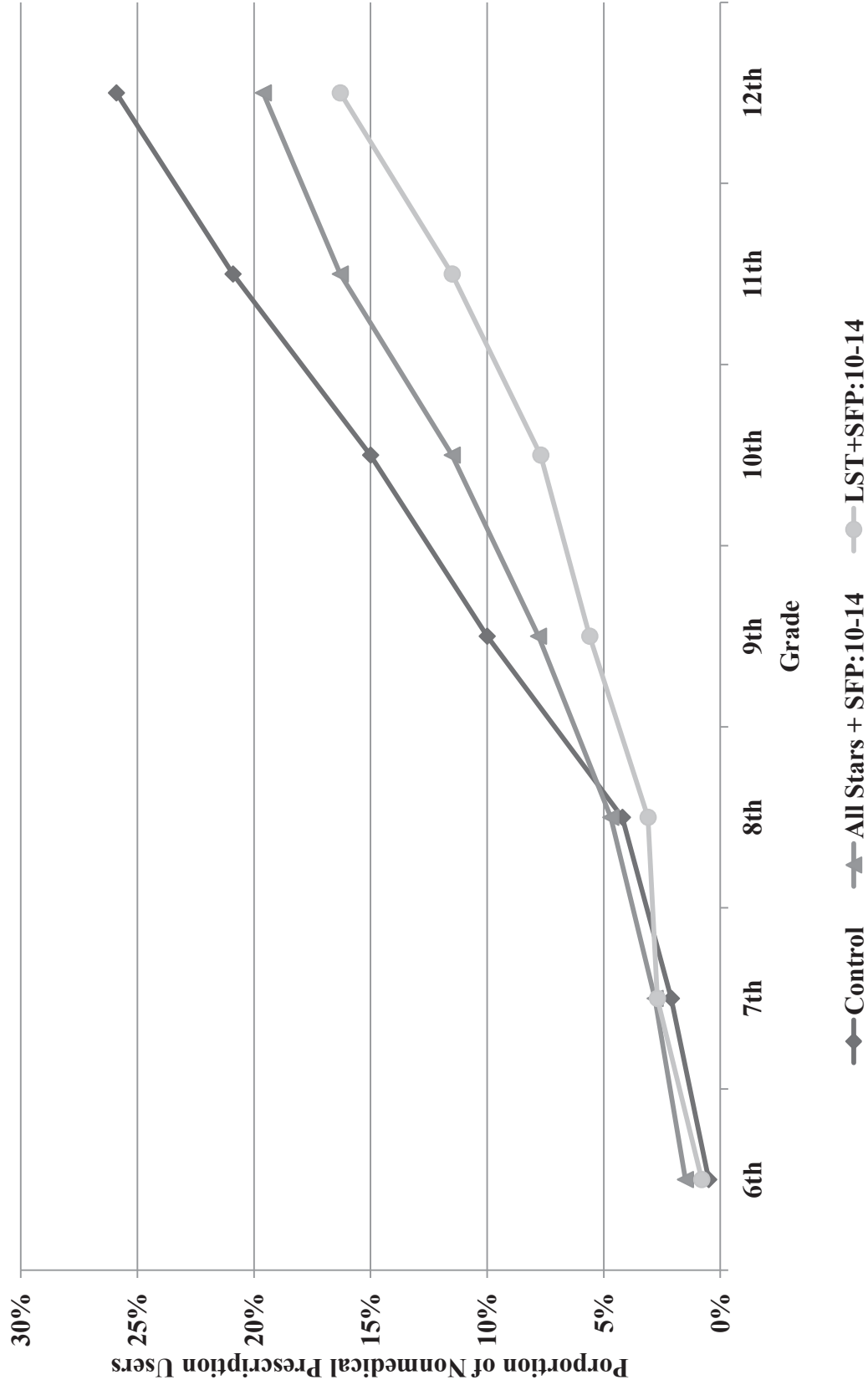


Figure 3: Prevalence of nonmedical prescription opioid use among student receiving combined school and family programs



**Trial Year from 2002-2010

Table 1: Prevalence of Prescription Opioid Misuse Across Programming Options

	Control	All Stars	LST	Project Alert	All Stars + SFP:10-14	LST+SFP:10-14	Project Alert + SFP:10-14
6 th	0.5%	0.5%	0.7%	0.7%	1.5%	0.8%	0.6%
7 th	2.1%	2.3%	1.8%	2.0%	2.8%	2.7%	3.7%
8 th	4.2%	5.9%	3.4%	4.5%	4.7%	3.1%	8.0%
9 th	10.0%	10.8%	7.6%	10.2%	7.8%	5.6%	14.8%
10 th	15.0%	15.2%	12.1%	14.4%	11.5%	7.7%	18.3%
11 th	20.9%	21.1%	16.4%	19.4%	16.3%	11.5%	22.9%
12 th	25.9%	26.5%	20.2%	23.3%	19.6%	16.3%	26.7%

LST=Life Skills Training; SFP:10-14 =The Strengthening Families Program 10-14, Trial from 2002-2010

Table 2: Effectiveness and Cost-Effectiveness of Program Conditions Compared to No Universal Program

	Estimate	SE	df	t	p	Incremental Effect ^A	ICER ^B (CI)
<i>School Program Versus Control Condition</i>							
All Stars v. Control	-.010	.014	113	-0.72	.475	1.7% (1.3, 2.1%)	--
Life Skills v. Control	-.053	.016	175	-3.24	.001	-4.4% (-3.9, -4.9%) ^T	\$613 (\$548, 693) ^T
Project Alert v. Control	-.023	.015	82	-1.47	.146	1.4% (0.1, 1.9%)	--
<i>School & Family Program Versus Control Condition</i>							
All Stars + SFP:10-14 v. Control	-.076	.028	744	-2.34	.020	-7.6% (-6.8, -8.5%)	\$4,923 (\$4,405, 5,552) ^T
Life Skills + SFP:10-14 v. Control	-.095	.037	292	-2.55	.011	-9.5% (-5.8, -10.5%) ^T	\$3,959 (\$3,525, 4,393) ^T
Project Alert+ SFP:10-14 v. Control	.016	.037	211	-0.04	.966	-1.6% (-2.6%, -.6)	--

^A= The change in predicted probability that a youth would report ever misusing prescription opioids before 12th grade

^B= The incremental cost of preventing a youth from ever misusing prescription opioids before 12th grade

^T= Below WTP threshold for preventing 1 youth from ever misusing prescription opioids before 12th grade

CI = 95% Confidence Interval

Can We Build an Efficient Response to the Prescription Drug Abuse Epidemic?

Assessing the Cost Effectiveness of Universal Prevention

Supplemental Materials

Appendix 1: The PROSPER System and EBPIs Included in Trial

The PROSPER delivery and support system links stakeholders from the state and local cooperative extension service (CES) and local public school systems for the purpose of implementing school- and family-based preventive interventions (Spoth et al., 2004). An embedded CES agent and a school official comprise the core of community prevention teams that involve multiple members representing various community interests. The local teams are supported by prevention coordinators in the CES and by university prevention teams (for a review, see Spoth et al., 2004). The teams each select from a menu of school and family evidence-based programs and offer those programs to youth and families within the community. Within the PROSPER dissemination trial three school programs were delivered (each community only delivers one of these programs): Life Skills Training, Project Alert and All Stars. Additionally, all PROSPER communities chose to deliver the Strengthening Families Program: For Parents and Youth Ages 10-14.

Project Alert. Project Alert is a school-based program that attempts to reduce substance use by targeting negative social influences that encourage use and promote social norms that reduce the likelihood of substance use. The program is comprised of 11 sessions that involve interactive activities such as role-playing, skills rehearsal and small group activities.

All Stars. All Stars is a school based program consisting of 13 sessions that seeks to promote healthy beliefs regarding drug use, create conventional norms against substance use, build strong personal commitments, facilitate school bonding, and increase parental monitoring. Activities are interactive, consisting of games, art activities, and small group discussions.⁴⁴⁻⁴⁶

Life Skills Training. Life Skills Training is a school based program that aims to prevent substance use and abuse by changing social influence and competencies. In particular, this

program seeks to teach social skills that build personal competence as well as facilitate assertiveness and refusal of substances across 18 sessions.^{37,47,48}

The Strengthening Families Program (SFP:10-14) 10-14. SFP:10-14 is a family-based program designed to reduce substance use and is grounded in a variety of family, resilience and biopsychosocial etiological theories. Families receive seven sessions (one per week) with parents and youth separated for an hour and then together (for an additional hour). The program seeks to reduce risk factors such as poor parental monitoring and bonding as well as issues of socio-emotional health.

Table 1: Baseline Demographic Characteristics

	Intervention	Control
Age	11.85 (.43)	11.82 (.42)
Gender (Male)	50.0%	49.2%
Dual Parent Family	50.2%	52.7%
Income	\$50,174 (32,994)	\$52,704 (42,762)

Appendix 1: Baseline (Fall 6th grade) Confounders Included in Propensity Models

Confounder	Brief Description
Youth-Level Confounders	
Prescription Opioid Use	<ul style="list-style-type: none"> • Ever use Vicodin®, Percocet, or OxyCotin®
Gender	<ul style="list-style-type: none"> • Target's Gender
Alcohol Use	<ul style="list-style-type: none"> • Ever had a drink of Alcohol
Ever been Intoxicated	<ul style="list-style-type: none"> • Ever been drunk from drinking alcohol
Level of Alcohol Use	<ul style="list-style-type: none"> • Alcohol use cumulative index
Inhalant Use	<ul style="list-style-type: none"> • Ever sniffed glue, paint, gas or others to get high
Hard Drug Use	<ul style="list-style-type: none"> • Ever used hard drugs or medications for someone else
Tobacco Use	<ul style="list-style-type: none"> • Have you ever smoked a cigarette.
Youth Substance Use Expectations	<ul style="list-style-type: none"> • Expectation for substance use
School Attitude	<ul style="list-style-type: none"> • Negative attitude toward school
Problem Solving Capacity	<ul style="list-style-type: none"> • Youth's ability to problem solve
School Adjustment	<ul style="list-style-type: none"> • School adjustment & bonding
School Attendance	<ul style="list-style-type: none"> • Target's School Absence
Refusal Efficacy	<ul style="list-style-type: none"> • Substance refusal efficacy
Refusal Intentions	<ul style="list-style-type: none"> • Substance refusal intentions
Stress Management	<ul style="list-style-type: none"> • Youth's ability to manage stress
Substance Use Norms	<ul style="list-style-type: none"> • Youth's perceptions of substance use norms
Future Use	<ul style="list-style-type: none"> • Youth's future substance use plans
Family-Level Confounders	
Parent Status	<ul style="list-style-type: none"> • Whether child lives with biological parents
Child monitoring	<ul style="list-style-type: none"> • Parent's knowledge about where child is, who they are with, their out of home behavior, disciplinary issues, child compliance.
Consistent Discipline	<ul style="list-style-type: none"> • Whether parents demonstrate consistent discipline with their child
Family cohesion	<ul style="list-style-type: none"> • The level of family cohesion (help each other, level of conflict, family planning, displays of aggression, orderliness, management of household)
General Child management	<ul style="list-style-type: none"> • How parents interact, discipline, supervise, and connect with children
Parents' Marital Status	<ul style="list-style-type: none"> • Whether parents are single, divorced or married
Enrolled in reduce lunch	<ul style="list-style-type: none"> • Whether the family uses a reduced or free school lunch program

Parent Activities with Child

- *Activities with child*

School-Level Founders

School Uses a Structured

Curriculum

- *The school's use of structured curriculum to teach skills and change norms for behavior.*

Percentage on Free Lunch

- *What percentage of your school's total student population is eligible for free or reduced cost lunches?*

Parent Outreach

- *In the past year, has your school made an effort to increase parental involvement in the school*

Community Pressure

- *There is pressure in the community to change things in the school.*

Teacher Resistance

- *Teachers in this school resist changes imposed from outside the school.*

Involvement of Agency

- *Agency Involvement in Youth Coalition*

School Attitude to Prevention

- *The degree to which the school's alcohol and tobacco policies emphasize prevention.*

District Attitude to Prevention

- *Principal's perception of district level attitudes toward prevention.*

Number of Teachers in School

- *How many full-time classroom teachers does your school have?*

Team-Level Founders

Extension Reputation

- *The degree to which the Cooperative Extension System is perceived to be a positive source of outreach to youth and families*

Team Size

- *Size of the PROSPER Team at Delivery*

Time for Parent Recruitment

- *The length of time needed for successful parent recruitment*

School's Prevention Attitudes

- *The School's attitudes and commitment toward prevention of students' problems, as a result of PROSPER*

Success of Community

- *Success of community's positive youth development coalition.*

Coalition

Appendix 2: Statistical Methods

In order to estimate the benefits of receiving the different programs delivered within PROSPER as well as the benefits of receiving multiple programs, a five- step analytic framework is employed (see Coffman et al., 2011). These steps include (1) defining the causal effects, (2) estimation of participant propensity to receive different program levels, (3) calculation and application of inverse probability weights to account for selection effects, (4) evaluation of the balance between program levels, and (5) outcome analyses of the impact of different program levels on ever using prescription opioids for nonmedical purposes.

Overall missingness was low and participation was similar to comparable longitudinal trials. The average missingness of an item was about 10.0% (SD=9.7%). Previous evaluations of PROSPER explored the study's missingness and found no evidence of threats to internal validity from differential sample attrition at grade 12. Multiple imputation was used to account for any missing data (STATA MI mvn)⁵⁰⁻⁵² This procedure uses an iterative Markov chain Monte Carlo (MCMC) method to impute missing values using a joint modeling approach under a multivariate normal model. The mvn approach uses estimates from the EM algorithm as starting values for the MCMC procedure. Twenty imputations were obtained and each imputation was drawn after a burn-in period of 100 iterations. The mvn procedure applied to handle missing data allowed for complete data analysis for both the propensity models and the outcome analysis.

Defining Casual Effects. The causal effects are defined using marginal structural models, which are models for potential outcomes.⁵³ Let s denote the school program, but now rather than $s = 1$ or 0 , s takes on the following values: $s = 0$ if the youth did not receive any school program, $s = 1$ if the youth received Life Skills, $s = 2$ if the youth received All Stars, $s = 3$ if the youth received Project Alert. As before, f denotes the family program and equals 1 if the youth received

SFP:10-14 and 0 otherwise. Thus, the potential outcomes are $Y(0,0)$ if the youth did not receive any of the three school programs or the family program, $Y(1,0)$ if the youth received Life Skills Training and did *not* receive the SFP:10-14, $Y(1,1)$ if youth received Life Skills Training and SFP:10-14, $Y(2,0)$ if youth received All Stars and did *not* receive SFP:10-14, $Y(2,1)$ if the youth received All Stars and SFP:10-14, $Y(3,0)$ if youth received Project Alert and did *not* receive SFP:10-14, $Y(3,1)$ if the youth received Project Alert and SFP:10-14. Note that again there is a monotonic function in that if a youth does not receive the school program they cannot receive the family program. Thus the potential outcome $Y(0,1)$ does not exist. The causal effects are the effect of receiving in Life Skills Training versus not receiving the school program $E[Y(1,0) - Y(0,0)]$, the effect of receiving the Life Skills Training and receiving the SFP:10-14 versus not receiving either program $E[Y(1,1) - Y(0,0)]$, the effect of receiving the Life Skills Training and SFP:10-14 versus receiving only the school program $E[Y(1,1) - Y(1,0)]$ (Research Question Grouping 4), the effect of receiving the All Stars versus not receiving the school program $E[Y(2,0) - Y(0,0)]$, the effect of receiving All Stars and receiving SFP:10-14 versus not receiving either program $E[Y(2,1) - Y(0,0)]$, the effect of receiving All Stars and SFP:10-14 versus receiving only the school program $E[Y(2,1) - Y(2,0)]$ (Research Question Grouping 5), (6) the effect of receiving Project Alert versus not receiving the school program $E[Y(3,0) - Y(0,0)]$, the effect of receiving Project Alert and receiving SFP:10-14 versus not receiving either program $E[Y(3,1) - Y(0,0)]$, the effect of receiving Project Alert and SFP:10-14 versus receiving only the school program $E[Y(3,1) - Y(3,0)]$ (Research Question Grouping 6). The marginal structural model for

the potential outcomes is given as:

$$E[Y_{ij}(s, f)] = \beta_0 + \beta_1 l + \beta_2 a + \beta_3 p + \beta_4 lf + \beta_5 af + \beta_6 p$$

Where l , a , and p are dummy variables and $l = 1$ if the youth received Life Skills and 0 otherwise, $a = 1$ if the youth received All Stars and 0 otherwise, and $p = 1$ if the youth received Project Alert and 0 otherwise. Thus, the causal effect given in Equations 4-12 are equal to:

4. $(\beta_0 + \beta_1) - \beta_0 = \beta_1$
5. $(\beta_0 + \beta_1 + \beta_4) - \beta_0 = \beta_1 + \beta_4$
6. $(\beta_0 + \beta_1 + \beta_4) - (\beta_0 + \beta_1) = \beta_4$
7. $(\beta_0 + \beta_2) - \beta_0 = \beta_2$
8. $(\beta_0 + \beta_2 + \beta_5) - \beta_0 = \beta_2 + \beta_5$
9. $(\beta_0 + \beta_2 + \beta_5) - (\beta_0 + \beta_2) = \beta_5$
10. $(\beta_0 + \beta_3) - \beta_0 = \beta_3$
11. $(\beta_0 + \beta_3 + \beta_6) - \beta_0 = \beta_3 + \beta_6$
12. $(\beta_0 + \beta_3 + \beta_6) - (\beta_0 + \beta_3) = \beta_6$

Because marginal structural models are models for the potential outcomes and not all the potential outcomes are observed, they cannot be estimated without further assumptions. Specifically, to estimate these models the assumption is made that there are no unaccounted for confounders influencing receipt of either the school or family programs, and thus, the causal effects are estimated using inverse probability weighted models for the observed outcomes.

Propensity Score Estimation Process. Within this project, two sets of propensity scores are estimated. Using multinomial logistic models, the propensity a person receives— (1) no

program, (2) the school program, and (3) the school and family program together, is estimated using a multinomial logistic regression. Because communities voluntarily picked one of the three offered school programs, a second set of propensity scores is then estimated for receipt of the different school-based programs also using a multinomial regression.⁵⁴ Both of these analyses were carried out using the GLIMMIX procedure in SAS 9.1³¹ that allows for specification of a link function, which for multinomial logistic and count data estimated here is log. This procedure also estimates error terms for non-normally distributed dependent variables. The propensity models to estimate these scores employ confounders across participant, organizational, infrastructure and community levels to predict program receipt and meet the stable unit treatment value assumption (SUTVA; described above). In order to test whether the logit link was appropriate, the Hinkley test was employed.⁵⁵ This test includes the logit propensity score squared as a covariate in the propensity model to test whether it is significantly related to the treatment condition in the presence of the other confounders.

In this study, propensity models were estimated for both the probability of participants being in the different school programs and the family program. Both models passed the Hinkley's test described above and were found to have suitable overlap.⁵⁵ Inverse probability weights were calculated and further diagnostics of balance were conducted. Unweighted and weighted standardized mean differences (SMD) between the control and treatment groups were calculated for each confounder in both propensity models.³⁰ Weighting generally lowered or maintained the SMDs of each confounder and no confounders had an absolute SMD above .2 when weighted, which is generally considered to be small.⁵⁶ Finding a small effect size across the confounders included in the model indicates that the different treatment groups are balanced and increases confidence in causal inferences.

Inverse Probability of Treatment Weight Calculation. Next the inverse probability weights for the combination of school program (IPW_s) and family programming (IPW_f) actually received by each participant are calculated. The IPWs are similar to survey weights and allow us to make adjustments to the sample data to account for selection effects affecting both school and family program receipt by up-weighting those who are underrepresented and down weighting those who are over represented.⁵⁷ When modeling multiple variables—such as the two types of program receipt considered here—the product of the variables’ weights is used.²⁹

Let $\hat{\pi}_{f0}$ be the estimated propensity to not receive the family program and $\hat{\pi}_{f1}$ be the estimated propensity to receive the family program. For youth who receive the family program, $wt_f = \frac{1}{\hat{\pi}_{f1}}$ and for youth who do not receive it, $wt_f = \frac{1}{\hat{\pi}_{f0}}$. Let $\hat{\pi}_l$ be the estimated propensity of receiving Life Skills Training, $\hat{\pi}_a$ the estimated propensity of receiving All Stars, and $\hat{\pi}_p$ the estimated propensity of receiving Project Alert. For youth who receive Life Skills, $wt_l = \frac{1}{\hat{\pi}_l}$. For youth who receive All Stars, $wt_a = \frac{1}{\hat{\pi}_a}$. For youth who receive Project Alert, $wt_p = \frac{1}{\hat{\pi}_p}$. The product, $wt_s * wt_f$ is the weight used.

Balance Evaluation. Next the balance of the different groups is evaluated before and after weighting to ascertain whether the adjustment using the IPWs successfully balanced the different groups. Balance was evaluated using standardized mean differences. Group overlap was also evaluated by examining boxplots of the distributions of the logit propensities by school and family program.

Outcome Analysis. The fifth step evaluates how receiving different amounts of programming impacts participant outcomes using the IPWs. In this case, prescription opioid

misuse is evaluated in terms of receipt of the school and family program as well as by each school program. To evaluate the effect of differential program receipt, I constructed two logistic models to examine differences between program receipt using the IPW estimation method.

$$\text{MS Model 1: } \textit{logit}[PR(Y)] = \beta_0 + \beta_1 l + \beta_2 a + \beta_3 p + \beta_4 lf + \beta_5 af + \beta_6 pf$$

For Model 1, β_1 is the effect of receiving either no programs vs. the school program, and β_2 is the effect of receiving the family program in addition to the school program. For model 2, β_1 is the effect of receiving Life Skills Training vs. not, β_2 is the effect of receiving All Stars vs. not, β_3 is the effect of receiving Project Alert vs. not, β_4 is the effect of receiving SFP:10-14 in addition to Life Skills, β_5 is the effect of receiving SFP:10-14 in addition to All Stars, and β_6 is the effect of receiving SFP:10-14 in addition to Project Alert. Thus the IPWs are employed to meet the assumption that no confounders are unaccounted for in the outcome analysis; these β 's, which correspond to those in the marginal structural models, can be interpreted as causal effects.

The outcome model, which is fit using the PROC GLIMMIX procedure, includes a binary outcome measure of whether youth had ever misused prescription opioids. PROC GLIMMIX allows a weighting function that may be employed to include the IPWs in the model and provides robust standard errors. This procedure allows for the inclusion of the two-level nested design of the model, with individuals nested within communities.³¹



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction Background and objectives	2a	Scientific background and explanation of rationale	3-5
	2b	Specific objectives or hypotheses	4-5
Methods Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Appendix 1
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	5-6
Sample size	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
	7a	How sample size was determined	5
Randomisation: Sequence generation	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
	8a	Method used to generate the random allocation sequence	5
Allocation concealment mechanism	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	N/A

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	Appendix 1
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6-7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	5
Recruitment	13b	For each group, losses and exclusions after randomisation, together with reasons	Flow Chart
	14a	Dates defining the periods of recruitment and follow-up	7
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Appendix 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8-9 Tables 1,2 & Flow Chart
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	8 Table 2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Table 2
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	8-9, Table 2
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	10-11
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	10-11
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11-12
Other information			
Registration	23	Registration number and name of trial registry	Trial Initiated before 2000
Protocol	24	Where the full trial protocol can be accessed, if available	Published Protocol
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	13

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.