2. Specific Aims

Cardiovascular diseases (CVD), specifically acute myocardial infarction (AMI) and stroke, are the leading causes of disability and death in the United States. (1) While significant progress in the prevention, detection and treatment of these diseases is apparent, much remains to be done.

Among the most effective approaches to diminishing AMI and stroke morbidity are primary prevention interventions designed to reduce first events. The reduction of cigarette smoking, control of hypertension and cholesterol lowering all contribute to recently observed reductions in CVD morbidity and mortality. (2) One prevention approach that has received increased attention recently is low-dose aspirin. In 1989, the Physicians' Health Study showed the benefit of low-dose aspirin in preventing AMI among healthy middle-aged men. (3) Similar results for stroke were found in the Women's Health Study. (4) There have been many additional controlled studies and, in a recent meta-analysis, investigators observed a significant 12% relative risk reduction in cardiovascular events achieved with aspirin use among healthy adults. (5) These and other data led the U.S. Preventive Services Task Force (USPSTF) in 2009 to publish an "A" recommendation in favor of aspirin use for primary prevention in men 45-79 years and women 55-79 years at increased CVD risk. (6) The recommendation was reinforced in the CDC Healthy People 2020 plan (7), the 'Million Hearts' initiative of the CMS and CDC (8) and recommendations from other authoritative bodies.

Increasing the appropriate use of aspirin in the population has the potential to achieve a substantial reduction of a first AMI in men and first stroke in women. This therapy is low-cost, safe and effective, yet many individuals who would benefit are not treated. We propose to evaluate a statewide campaign using innovative methods to educate the public and health communities about appropriate aspirin use. In the context of a multi-million dollar (see attached letter of support), philanthropically funded, statewide campaign, we will test the impact of mass media and health system interventions in a group-randomized trial. In addition to the primary goal of increasing appropriate aspirin use, we will add to public health experience using innovative population-based approaches for disease prevention and provide a model for wider dissemination.

Specific Aims:

1. Measure self-reported aspirin use for CVD primary prevention at baseline in random samples of Minnesota and Upper Midwest men ages 45-79 and women ages 55-79 years.
2. Disseminate a statewide mass media and health system interventions in a two-arm group-randomized research design within 24 geographic Minnesota units (12 study pairs).
3. Evaluate the individual and combined effectiveness of a mass media approach and a media plus a targeted health system intervention on appropriate aspirin use in adults (men age 45-79, women age 55-79).
4. Measure intervention sustainability at year 5 by withdrawing program support for the health system intervention in year 3 from the 12 original geographic areas.
5. Assess program generalizability of the health system intervention by applying the intervention in year 3 to the original 12 comparison areas.
6. Assess secular aspirin use trends in adjacent Upper Midwest states.
7. Monitor the effects of this primary prevention program on hospital admission rates for AMI, stroke and aspirin-related adverse events (e.g. gastrointestinal bleeding and hemorrhagic stroke).
8. Assess the cost-effectiveness of the intervention program.

Hypotheses:

Primary: The combined health system and media interventions will increase appropriate aspirin use for primary CVD prevention by absolute 15% in comparison to baseline against a secular trend of 1% per year.
Secondary: Measurable differences will be detected between the intervention strategies.

a. Mass media alone (+5%).
b. Health system intervention (+10%).
c. The intervention effects will be sustained at year 5.

3. Research Strategy

(a) Background:

Disease Burden

The major cardiovascular diseases, AMI and stroke, are leading causes of disability and death in the United States. (1) Minnesota has a reputation as one of the healthiest states in the nation. (9) Yet, the cardiovascular disease burden in Minnesota is large with over 23,000 hospitalizations for AMI and stroke in 2009 among adults age 45-84 years and (10) direct annual hospital costs in excess of $500 million.

The State of Minnesota, similar to other United States regions, has a substantial high-risk population.

For example, the prevalence of hypertension is 39% for men and 43% for women in the 45-79 and 55-79 year age categories, respectively. (11) In the same age ranges, the median serum cholesterol is 199mg/dl for men and 215mg/dl for women. (12) These data suggest that more than half of adults are above the recommended level of ≤200 mg/dl. (12) Cigarette smoking is now 10% among men and 11% among women, but self-reported diabetes has increased to 12% for men and 10% for women age 65-74. (13) The high prevalence of classic atherosclerosis risk factors defines this age range as a high-risk population foe AMI and stroke. From a public health perspective, prevalent high-risk with known high rates of adverse outcomes should be addressed through population-wide prevention approaches.

Aspirin for Primary Prevention of Cardiovascular Disease

Atherosclerotic disease, the major cause of AMI and stroke, is a chronic arterial inflammatory disorder in which metabolic and other risk factors initiate and propagate arterial remodeling and plaque formation. (14) Thrombosis of the arterial system is a consequence of plaque rupture leading to arterial occlusion and associated AMI or stroke. (15) Platelets play the key initial thrombotic role in the repair of an injured artery. Unfortunately, this normal defense mechanism may be pathologic and lead to occlusion of a coronary or cerebral artery. Death of myocardium or brain occurs rapidly, often before acute hospital-based medical interventions can be initiated. (15) Anti-platelet medications block platelet activation and reduce or prevent thrombosis. This benefit is, in vulnerable individuals, balanced by the adverse effect of increased bleeding.

Aspirin, among anti-platelet agents, acts by blocking the cyclooxygenase (COX) activation system of prostaglandin H (PGH) synthase 1 and synthase 2. These are also referred to as COX-1 and COX-2. Low-dose aspirin inactivates COX-1 while higher doses inhibit both COX-1 and COX-2. (16) Platelet aggregation is inhibited by aspirin.

The idea that aspirin could prevent heart attacks dates at least back to the 1940's when a California practitioner and University of Minnesota medical graduate, Dr. Lawrence Craven, noted a connection between nosebleeds and aspirin use in children. (17) He described his observations in 1950 suggesting that aspirin might prevent AMI. (18) The first formal clinical trial to test the benefit of aspirin for secondary prevention was published in 1974 and many other trials followed, establishing the efficacy of aspirin during and after an AMI.

(19) Evaluation of the efficacy of aspirin for primary prevention of CVD stems from several very large randomized clinical trials. The Physicians' Health Study (PHS) randomized 22,071 male physicians ages 40- 84 to every other day aspirin. (3) There was a 44% reduction in the risk of AMI (relative risk, 0.56; CI, 0.45 to 0.70). This benefit was associated with a non-significant increase in bleeding as manifested by stomach ulcers and hemorrhagic stroke. The Women's Health Study randomized 39,876 healthy subjects age 45 and above to 100mg of aspirin daily. (4) At 10 years follow-up there was a 17% reduction in the risk of stroke in the aspirin group, as compared to placebo (relative risk; 0.83; CI, 0.69 to 0.99). There was no effect on coronary heart disease mortality in the whole study population but subgroup analyses demonstrated that aspirin significantly reduced the risk of major cardiovascular events, including ischemic stroke and AMI, among women 65 years of age or older. Again, a small increase in stomach ulcers and a non-significant increase in hemorrhagic stroke were observed. These and other smaller studies demonstrated a net benefit of aspirin in a meta-analysis. (5)

More recent studies in populations with diabetes and asymptomatic peripheral artery disease have produced mixed results. There were non-significant trends toward benefit in those with diabetes but no effect among patients with peripheral artery disease. (20,21) These studies were much smaller than the positive trials and limited to selected subgroups well treated for cardiovascular disease risk.

These and other data led the USPSTF in 2009 to recommend increased use of aspirin for primary prevention in men ages 45-79 years and women 55-79 years after appropriate medical consultation. (6)

Communication Media and Health Campaigns

Mass media and other communication strategies are commonly used to promote positive health behaviors

and to prevent disease. Health promotion and intervention campaigns often use communication media to deliver persuasive messages to populations. (22,23) As with most such campaigns that focus on individual behavior change, much of the work in health communication integrates social-psychological based persuasion and communication theory to understand how media shape health attitudes, opinions, and behaviors. (24-26) Unlike earlier campaigns in the days of "analog" media, communication strategies converging today in digital media offer the potential to generate even greater communication effects. (27)

Recent communication research suggests that media campaigns that "spark" relevant health-related discussions among target audiences increase a health campaign's reach and influence. (22,27,28) Hornik noted that interpersonal discussions of campaign messages were more effective in eliciting behavior change than simple exposure to messages alone. (29) Digital communication tools available can maximize this kind of interactivity, among laypersons and healthcare providers alike. (30-32)

Recent studies also demonstrate that health-related media messages produce more consequential behavior change when such messages prompt interpersonal discussions and information exchange among target audience members. (29,33,34) In this frame of reference, the impact is the stimulation of discussions arising from media messages in a two-step flow of communication (35) wherein individuals receive information from a media source (step one) and then share the information within others in their social network (step two). Within the health communication domain, this process is known to increase the role of the personal influence (27,32) while extending the reach and impact of the media campaign. (30,31) Thus, health campaigns aimed at attitudinal and behavior change should incorporate strategies to stimulate target audiences to discuss relevant health information within their social networks. The advent of online media, which includes open- access information sharing and discussion, offer a potentially more effective way to accomplish this goal. The approach offered here includes an added dimension of interactivity, using the mass and digital media techniques to promote discussion between healthcare providers and the population. (36)

Health System Interventions and Health Professional Education

The benefits of evidence-based recommendations can only be realized if they are effectively translated into clinical practice. Primary care physicians provide more outpatient visits than all specialties combined, emphasizing the importance of community-based practice settings as a focal point for disseminating approaches to prevention. (37) Aspirin recommendations are widely disseminated, however, a clinical care gap exists in the use of aspirin that is especially wide for primary, as compared to secondary, prevention. (38,39)

Although the public accesses healthcare information from a wide variety of sources, most adults continue to rely upon their physician and other healthcare team members as trusted sources of healthcare information.
(40) Public and health professional focus groups and surveys chartered for the current proposal confirm that in Minnesota communication with a primary care provider remains an important mechanism for initiating behavioral change (see below). Recent data from a Wisconsin primary care population demonstrate that aspirin is underutilized for primary CVD prevention in the high-risk target population and overused by the low risk population. (38) Thus, health system interventions must target the primary care site.

The multicomponent health system intervention outlined in this proposal will disseminate accurate, evidence-based cardiovascular health information that aligns with the public mass media campaign. The media campaign will elicit patient queries to Minnesota health professionals. This system intervention will ensure that health care system practices have prepared, proactive office-based care teams that can rapidly evaluate the individual benefit and risk of aspirin use in the target population. Our work completed to date assures that these teams can provide such aspirin prescriptions easily in a busy office environment.

Because most adults receive preventative care from primary care physicians (not cardiovascular specialists), we have designed a series of interventions that target the community primary care practice as the logical focal point for implementing strategies that improve aspirin prescription and use. Practical intervention strategies have been recommended to ensure that the latest and most effective scientific recommendations are rapidly translated to the community. (41,42) This approach is endorsed by leading State medical organizations (see attached letters of support).

Challenges with the organization and delivery of health care services contribute to the nation's inability to reach current evidence-based goals for optimal chronic disease control. (8,9) Among large medical groups, fewer than half have implemented improvement tools such as use of registries, tracking systems, case managers, feedback to physicians, or clinical guidelines with reminders, whereas other systems lack

the technology necessary to sustain quality improvement efforts. (43-46) Simultaneously, many contemporary prospective intervention studies are limited by inadequate sample size, lack of subject enrollment from real world care settings, lack of control subjects, or limited scope of implementation within a single medical group or health system. (47) Although some trials of quality improvement strategies have demonstrated improvements in the process of care delivery, demonstrating improvement in clinical outcomes has been more challenging. (48,49) The paucity of effective interventions for improving care in primary care settings provides a rationale for the current study which serves as a "pragmatic clinical trial" to test whether implementation of an organizational intervention could improve aspirin prescriptive behaviors in primary care. (50)

(b) Significance:

The epidemic of AMI and stroke continues. The United States remains a high-CVD risk culture based on prevalent atherosclerosis risk factors. Prevention is recognized as the best approach to reducing these chronic diseases. Low-dose aspirin has a 30-year history of proven benefit for primary prevention of heart attack and stroke when evaluated in clinical trials. The promotion of targeted aspirin use is accepted as a national health recommendation by multiple independent, authoritative bodies. However, new health recommendations do not necessarily spread into population use naturally or quickly. The traditional media has served as one method of disseminating such health messages, but in the absence of massive advertising budgets (e.g., Nexium, 'The Purple Pill', $400 million/year), the effects of health education campaigns for disease prevention are modest, at best. We propose to add a health systems approach to a statewide mass media campaign in a research design that will explore the effects of these strategies and provide information to inform future health campaigns. To our knowledge, the current proposal represents the only effort to measure the effectiveness of translation of the USPSTF aspirin recommendation to a real world population. This campaign thus has the potential for significant public health benefit by improving appropriate aspirin use and discouraging inappropriate use.

(c) Innovation:

This approach is innovative in several ways. First, as stated, to our knowledge this is the first effort to advocate and evaluate this USPSTF cardiovascular primary prevention recommendation at the population level; our state and university team are uniquely positioned to achieve this population health goal. Second, we have proposed use of a unique combination of educational approaches that include the most contemporary concepts underpinning effective use of mass media and health system intervention, which should provide a reliable measure of practice change efficacy that extends far beyond what was long attempted using traditional continuing medical education. Third, we have created a scientifically rigorous study design to be implemented at the population level, thereby accruing the advantages of a "real world" application, and enhancing its generalizability to other regions of the country. Finally, we propose use of a group randomized trial design, which is challenging, but appropriate and operationally achievable. The price of this approach is a large sample size with many geographic areas. Nonetheless, we believe that this method has the greatest likelihood of demonstrating important population-based effects.

(d) Approach:

Pilot Studies

Minnesota Heart Survey (Self-Reported Aspirin Use): Since 1980, the Minnesota Heart Survey (MHS) has conducted 5-year surveys of 3,000-6,000 randomly selected healthy adults. (39) A question on the use of aspirin for cardiovascular disease prevention was asked from 1980 until 2009 (the most recent survey). Increases in aspirin use were observed (Figure 1). These data serve as the basis of our sample size determinations and estimation of secular trends.

Physician and Public Aspirin Cardiovascular Prevention Studies:

To plan the interventions, focus groups and a survey were undertaken among practicing primary care physicians and a general population sample representative of the target ages (2011).

<u>Practicing physician aspirin attitudinal survey</u>

Physicians were aware of the use of aspirin as a primary prevention for cardiovascular disease. They do recommend low-dose aspirin for their patients if they feel it is appropriate according to guidelines and their knowledge of the patient. They tend not to "push" aspirin on patients but do "encourage" aspirin use if asked. They recognize that many of their patients start aspirin without advice and they only learn about it later. While physicians were aware of potential bleeding complications, they reported no personal

experience of patients with serious bleeding associated with aspirin. In summary, Minnesota physicians expressed positive attitudes about aspirin use but were not active in recommending it for their patients.

General public

We conducted public focus groups and a statewide population-based web survey of 600 age-appropriate individuals by Padilla Speer Beardsley, a survey and communication consulting firm.

In five focus groups of ten participants each, questions focused on media sources for health information and attitudes/practice towards aspirin use. The findings of the focus groups and the web-based survey were similar. Most members of the public described their own physician as the primary source for health information, although many also use websites, family and friends, television and printed materials. Many said they did not pay attention to health advertising. They preferred to communicate directly with their health professional in person or by phone. They had a very positive attitude about aspirin as a preventive intervention, with 69% believing in its effectiveness. Seventy-five percent said they would take aspirin, but only if their doctor recommended such use. Twenty percent cited the Bayer company campaign as a reason for taking aspirin. The summary survey report is attached as Appendix 1. These data inform our campaign.

Community Pilot Study: Hibbing, MN

In 2012, a pilot study was initiated to test the intervention components and evaluation procedures in the community of Hibbing, MN. Hibbing has a population of 16,231 (2010 census) with a medical referral area 2-3 times that size. It includes one hospital and three competing medical group practices plus a VA clinic. Hibbing is a center for taconite mining and merchants serving the surrounding communities. We tested mass media (print, billboards and radio), web-based social media, physician and health professional education, a medical record based aspirin candidacy tool and other tools to facilitate indication screening, with a prescriptive reminder system. We also engaged community leaders.

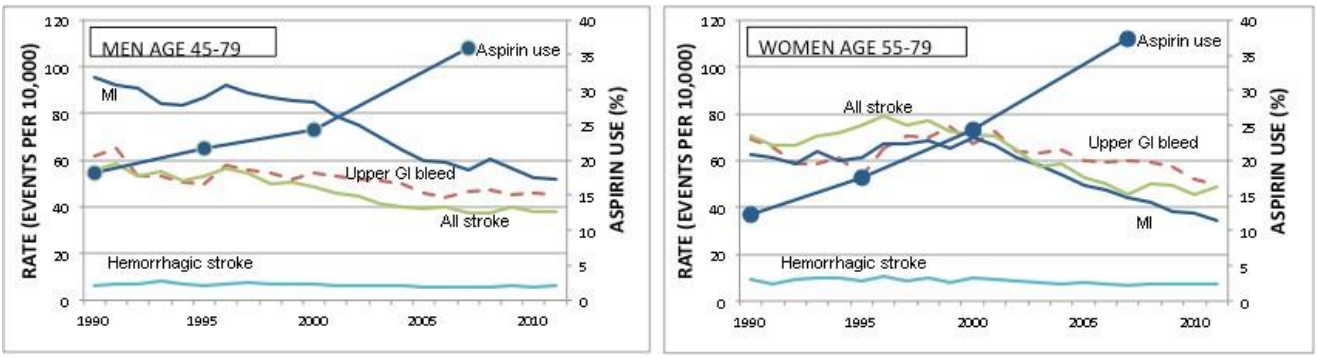
Baseline, 4-month and 18-month follow-up telephone surveys of randomly selected adults (men aged 45- 79 and women 55-79) resulted in participation rates of 60%. Questions regarding aspirin use for primary prevention and related medical conditions were asked. From baseline to follow-up, aspirin use for primary prevention increased significantly from 37% to 52%. A subsequent 18-month follow-up after the campaign was over showed no decrement in aspirin use (52%). Most individuals were aware of the campaign and many had discussed aspirin with their physicians. We also tested a biochemical validation of self-report of regular aspirin use, thromboxane B_2. We found misclassification to be minimal. This confirmed our earlier work on the validity of self-reported aspirin use surveys. (51)

This substantial pilot study confirmed the feasibility of entering communities, obtaining the support of health professionals and their organizations, achieving message penetration for the general population and in eliciting measurable health behavior change as evidenced by increased aspirin use. This pilot study leaves us with considerable experience and tools to apply in the statewide expansion. The pilot data also informed our communications media campaign, which has been further refined based on the Hibbing experience and additional focus groups (Appendix 2).

Population surveillance of aspirin adverse effects

An important concern regarding promotion of wider use of aspirin therapy is the association of the anti-thrombotic adverse effects of upper GI bleeding and hemorrhagic stroke. Utilizing the data from the Minnesota Hospital Association system by coding all UB-04 claims data from seven county metropolitan area hospitals; we have compared trends in aspirin use from 1990 to 2011 in the target age categories and hospitalizations for serious gastrointestinal bleeding and hemorrhagic stroke (Figure 1). As shown, while aspirin use has increased since 1990 (men: 18% to 37%, women: 12% to 38%), there is no similar increase in either hemorrhagic stroke or upper GI bleeding requiring hospitalization. The adverse event trends are either downward or flat. Of course, these population data do not provide causality inferences as many other factors may affect bleeding trends. However, there is no indication of increased prevalence of hemorrhagic stroke or upper GI bleeding in a large metropolitan area associated with widespread increases in daily aspirin use.

Figure 1.



Practice based research network

The Center of Excellence in Primary Care (CEPC) at the University of Minnesota Medical School and the Minnesota Academy of Family Physicians Research Network (MAFPRN) will provide expertise in dissemination science essential for effective implementation in community practices. As a cooperative program between Family Medicine, General Internal Medicine, and Pediatrics, the CEPC works with Practice- based Research Networks (PBRNs) to speed the adoption of innovation in primary care. A national leader in practice-based research, the CEPC developed the TRANSLATE model which has been used successfully to support practice redesign resulting from new guideline implementation. (52,53) Working closely with the MAFPRN, a network of 230 community-based primary care providers in 155 practices throughout Minnesota, the CEPC provides practices with 'boots on the ground' support for practice redesign using Practice Facilitators certified through a 14 week curriculum as effective primary care change agents. (54) (http://www.millardfillmorecollege.com/practice_facilitator_ad) The Practice Facilitation model has been shown to promote rapid adoption and improvement in primary care delivery by focusing on building organizational capacity within practices for continuous improvement. (55-57)

For over thirty years the MAFPRN has supported studies addressing a wide variety of topics important to primary care. From small "bottom up" observational studies, to practical clinical trials evaluating practice change to large landmark clinical trials in cardiovascular disease and diabetes, the MAFPRN has been successful both in engaging clinical practices and translating innovation into practice change. (53,58-60) The MAFPRN members are early adopters and leaders in the primary care community, and provide an excellent resource for dissemination of new findings to practices and clinical systems throughout the state.

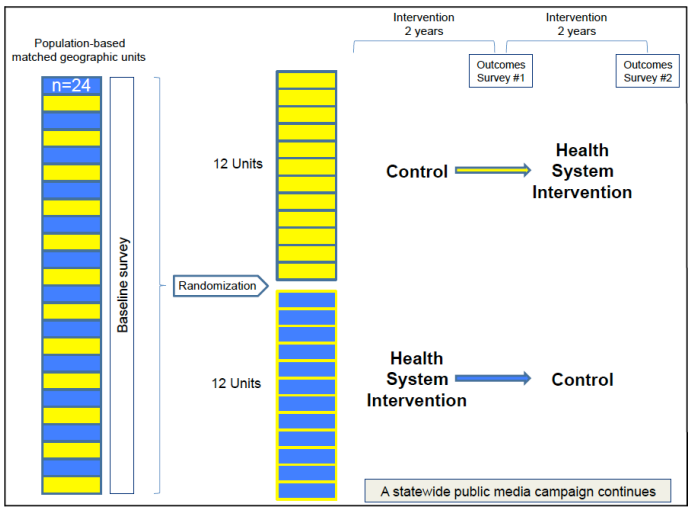
Community advisory board

Recognizing that an effective statewide campaign would require support from a variety of health-related organizations, we have organized an advisory board comprised of representatives of all major statewide stakeholder organizations. We will utilize their support for the aspirin campaign and the research proposed in this application. The group includes representatives from the Minnesota Department of Health, Minnesota Medical Association, Institute for Clinical Systems Improvement (ICSI), national American Heart Association, American College of Physicians (Minnesota Chapter), American College of Cardiology (Minnesota Chapter), Minnesota Academy of Family Physicians, Preventive Cardiology Nurses Association, Area Health Education Centers (AHEC), Minnesota Community Measurement, Berman Center for Outcomes in Clinical Research, Clear Channel Outdoor Advertising, Blue Cross/Blue Shield of Minnesota, HealthPartners Research Foundation and North Point Health and Wellness Center. This groundwork will facilitate the intervention campaign beginning on schedule. Letters of support are attached.

Overview of the Research

The proposed Dissemination and Implementation Research will test an innovative health system intervention in the context of a statewide media campaign. In a two-arm design (Figure 2), the education programs will advocate appropriate aspirin use for primary prevention of cardiovascular disease. With a primary endpoint of regular low-dose aspirin use, the research will apply innovative strategies in a real world setting and provide data to design prevention programs. The multidisciplinary research team has the background, skills and experience to successfully meet project goals.

Figure 2: Study Design

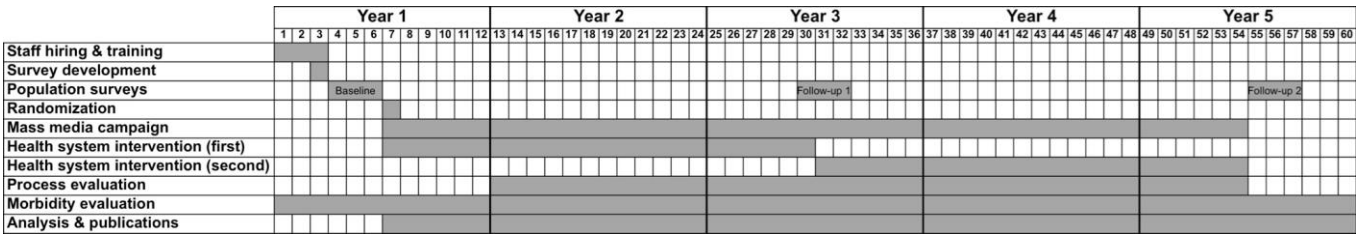


Research Design

We propose a group-randomized trial (GRT) to evaluate two interventions, a media communications campaign and a health system approach to enhance the effectiveness of care providers to improve appropriate aspirin use among men age 45-79 and women age 55-79. GRTs are characterized by the random assignment of identifiable units rather than individuals to study conditions, with measurements taken on the members of those groups to assess the impact of the intervention. (61) GRTs are appropriate whenever the investigator wants to evaluate an intervention that manipulates the physical or social environment, involves social processes, or cannot be delivered to individuals without risk of contamination. GRTs are the gold standard in public health and medicine for evaluation of an intervention that meets any of these criteria. (61-64) In this proposal, the groups are 24 defined geographic areas in the State of Minnesota.

In particular, we propose to evaluate the independent effects of the media intervention and the joint effects of media plus a health system approach. We define pairs; each containing two matched geographic areas (see below), from a total of 24 areas. (Appendix 3) We will randomly assign one area of each pair. We will collect data from independent random samples of 100 age-eligible residents from each area at baseline and at two follow-up surveys. This is a nested cross-sectional design, as different residents will be measured at each survey, with residents nested within geographic areas, and areas nested within study conditions. (61) The initial intervention following randomization will last two years. The active support of the health systems will then be withdrawn from the initial 12 areas. A survey two years later will evaluate sustainability. The health systems support will then be applied to the previous media only controls to evaluate generalizability. (Figure 2)

Timeline



Sample Selection and Randomization Procedures

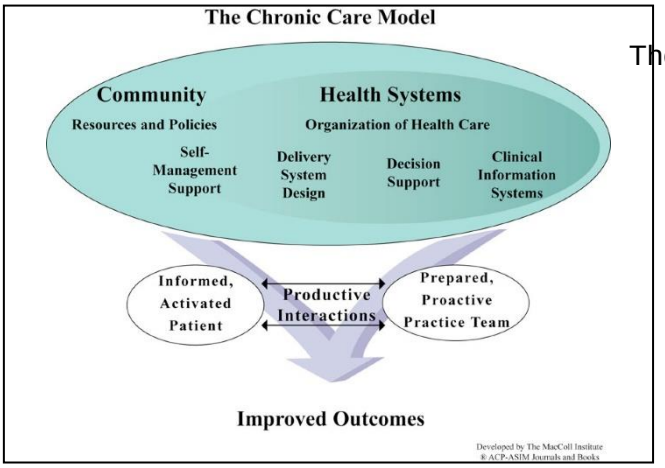
The state of Minnesota will be divided in 24 dispersed geographic areas, each being centered on a clinic or clinics serving a defined catchment area. In collaboration with the University of Minnesota Population Center, our selection will be based on identification of cities with clinics and separated by about 100 km. This precludes the use of the large urban areas in the Twin Cities and Rochester areas for which contamination could not be contained. The selected centers will be sorted by readily available demographic characteristics such as population size, age structure and income, and adjacent pairs tentatively accepted as a pair to be randomized to intervention or control status. We expect that large populations (for example, Saint Cloud and Duluth) will be paired. For smaller centers these tentative pairs will be examined for being dispersed but also in the major geographical areas of SE, S, SW, W, NW and N

Minnesota. This will help control for different cultural and occupational characteristics in these regions of Minnesota. Because randomization will occur only after the first survey, judicial re-assignment of pairs may be used to over-ride any tentative pairs based solely on the sort order. The accompanying map of Minnesota illustrates (without showing pairings) the dispersed nature of our selection process (Appendix 3). For illustrative purposes only, rectangles have been drawn around a possible (non-programmatic) selection. Although pairing will be used to control variation between the intervention and control conditions, the pairs will be ignored in the analysis because of the reduction in the degrees of freedom of the proper error term in the matched analysis (df=11) compared to the unpaired analysis (df=22). (65)

Educational Interventions

The education program has two elements: 1) mass media and 2) a health systems intervention approach that includes health professionals, primary care clinics, and community support. These were informed by current education theory (Figure 3), focus groups and population surveys. These interventions were tested and modified after the Hibbing pilot study. Funded by private donors, the program also enjoys strong support from the Minnesota Department of Health and other statewide health organizations, facilitating program emplacement and provider uptake (see attached letters of support). The intervention programs, currently planned for the dissemination research, are described in brief below.

Figure 3: The Chronic Care Model



Mass Media Component

The mass media intervention is anchored in theory and research to develop a statewide campaign strategy that delivers key aspirin messages through a variety of awareness-building media formats including television, print, and radio. (25,28,29) The strategy integrates well-established media/public relations and advertising tactics, providing a mix of news coverage, public service announcements, and targeted messaging throughout the intervention and evaluation phases. (24) The mass media campaign is expected to draw issue attention, raise awareness, and increase thinking about cardiovascular health. (22,23) A separate online media campaign serves as a unique media intervention (described below). Formative data have been collected using focus groups and surveys. The data are used in conjunction with extant literature to develop key messages, strategies, and tactics for the media campaign. The strong relationships between the University, news organizations, and healthcare professionals uniquely position this interdisciplinary team to leverage a statewide mass media campaign. The campaign will engage the entire state.

The media mix will include TV, radio, and print advertising with an annual budget of $500,000. This is expected to produce over 24 million gross impressions statewide per year with a cost per thousand impressions (CPM) of $20.83. The elements in this campaign, refined by the Hibbing experience, are found in Appendix 2.

Online Media

The online media are another form of mass media including a range of interactive media tools that permit users to simultaneously seek, consume, discuss, share, and analyze cardiovascular health information. As such, the online media platforms will offer individuals dynamic, interactive environments to explore, find, share, and discuss cardiovascular health information in ways known to engage users and support behavior change. (36, 66-68) Specifically, a web-based site offers expert cardiovascular health-related information, key messages developed in tandem with the larger campaign, links to news articles and related information, links to clinics' and healthcare professionals' websites, options for asking questions, sharing information, etc. (Appendix 4) Several search engine optimization techniques will be used to direct traffic to the site, including links from highly visited sites in the intervention communities (e.g., city or county health department sites) and direct links from clinics and healthcare providers participating in the professional education intervention.

The online media campaign will use the other media exposure combined with online promotion strategies to drive online media awareness and impressions in the online media intervention.

Health System Interventions and Health Professional Intervention:

The primary goal of the health system intervention is to increase the appropriate use of low-dose aspirin within the primary care clinical environment. The proposed intervention is designed to improve prevention practice within several domains of the Chronic Care Model. (69) The intervention is modeled after the TRANSLATE model used successfully for dissemination in clinical trials of both diabetes and chronic kidney disease guidelines. (70)

All clinics in the intervention arm will receive print materials, including posters and brochures, to support patient awareness of program goals. Pocket cards have been prepared that will be distributed to the clinics to be used by their health professionals in evaluating appropriate aspirin use for their patients.

Specifically, the health systems practice intervention focuses on establishing electronic 'aspirin registries' supported within practices by a health care coordinator providing proactive clinical decision support. The intervention includes the following components: (a) contractual health system administrative relationships to support the intervention; (b) dissemination of aspirin candidacy identification tools to facilitate adoption in Electronic Health Records (EHRs) and data warehouses of standardized electronic identification, tracking, and reporting of primary prevention aspirin candidacy; (c) an online Continuing Medical Education (CME) accredited aspirin prescriptive educational intervention (Appendix 5) and tools to provide Maintenance of Certification requirements for primary care providers participating in the aspirin campaign; (d) 5-6 regional "Practice Facilitators" working with clinical practices in intervention areas to facilitate change through academic detailing, staff training, and local community engagement, (e) a pharmacy-based promotion of aspirin. This multicomponent intervention strategically targets components from across the Chronic Care Model. (69) The model builds on the extensive infrastructure already established by the Minnesota legislature mandating adoption of EHRs, public reporting of selected Quality Improvement Measures (Minnesota Community Measures), and the introduction of local care coordinators through patient centered medical homes and other new models of care delivery.

Health system administrative engagement:

Based on our pilot experience, a signed Memorandum of Understanding (MOU) will be secured between the University of Minnesota and health systems' administration. A MOU template is attached. (Appendix 6)

Electronic medical record (EMR) and manual aspirin candidacy tools:

In the health systems randomized to intervention, we will offer support for adoption and integration of an open source aspirin registry providing clinical decision support for aspirin candidacy identification tools.

Electronic medical record candidacy tool: In 2012 more than 85% of practices in Minnesota had adopted EHRs. (71) While each EHR may vary in the method of registry integration, all EHRs certified by the Office of the National Coordinator (ONC) must have the ability to provide registries and population based reports. Our specific aspirin EHR registry work provides two major approaches for adoption: 1) support for integration of data standards for aspirin use into their existing EHR registry or data warehouse, or 2) use of an open source aspirin registry provided by the University of Minnesota. An open source aspirin registry was developed by University of Minnesota researchers as one component of a Population Health Management software suite.

The aspirin standards and software are available without charge to all users. For the pilot, a commercial vendor (Omicron Health Systems, Inc. Minneapolis, MN) provided technical support for St. Luke's EMR systems for installation and management of this tool. The registry enables efficient identification of aspirin candidates as defined by Aspirin Candidacy Measure. (Appendix 7)

Manual aspirin candidacy patient identification tool: For those clinics and health systems that do not utilize an electronic medical record, the senior clinic administrator will identify a site coordinator and local physician champion (LPC). A small sticker will be affixed to medical records of patients who are aspirin candidates as defined by gender and age-based criteria (excluding individuals with a history of gastrointestinal bleeding or aspirin allergy). The sticker provides a reminder to providers and staff that the patient is an aspirin candidate. This manual aspirin candidate selection system will utilize the simple algorithm as defined in Appendix 7.

In our Hibbing pilot, we have demonstrated that use of either the manual or EHR aspirin candidacy decision support tools was associated with a doubling of prescription of aspirin, and this was effectively focused on increasing use in appropriate aspirin candidates. Appropriate aspirin prescriptions increased from 39 to 80% with the EHR tool, and from 37 to 65% with the manual tool, over a 12-week period. (Appendix 8)

Educational intervention

Increasing the appropriate use of low-dose aspirin within the primary care clinical environment is supported via a specific health professional education program providing Maintenance of Certification and Continuing Medical education (CME) credits. A webinar (Appendix 5) for use in training health professionals has been developed in cooperation with the Academic Health Center Learning Commons, the School of Public Health, and the office of Continuing Medical Education. Health professionals completing the webinar will complete a pre- and post-assessment so learning can be measured. https://umconnect.umn.edu/p63007925/ These health professional educational sessions will be used by staff at each intervention site as: (a) an annual training mandate for professionals at each participating health system, as outlined in our "Memorandum of Understanding" with the health system, and (b) as a source of CME physician, nursing, and pharmacy credit. The seminar and webinar series was created in partnership with a regional CME committee that included health professional faculty representing cardiovascular medicine, internal medicine, family medicine, pharmacy, and nursing. These instructional modules (including use of live "lunch and learn" seminars and video conferencing) were created with four pre-defined learning objectives and were evaluated using sequential pre-seminar and post-seminar testing during the Hibbing pilot study. This pilot demonstrated the positive learning module efficacy in 66% of the nursing and 50% of the physician work force in Hibbing.

For primary care providers in Family Medicine, Internal Medicine, and Pediatrics, Maintenance of Certification credit will be provided for completion of Part IV requirements for Board re-certification upon 12 months of participation in an active campaign with their medical practice of promotion of appropriate use of aspirin. Providers must show active participation and attend educational activities at least once per quarter.

Academic detailing:

Under a model long utilized by the pharmaceutical industry, we will hire and train 5-6 geographically distributed Practice Facilitators (PF). PFs are usually health care or related professionals who provide assistance to several community practices at a time with research and quality improvement activities. Ideally, PFs operate from an empowerment framework that seeks to develop the capacity of providers, staff and administrators in a practice or organization to implement planned changes in their organization and sustain it over time. PFs can provide access to expertise on specific topics that a particular organization finds helpful, provide structure and focus to system change, and support clinical research efforts. By providing basic training for an organization, and by assisting practitioners with new tools and methods, PFs provide motivation and build confidence in practices to facilitate rapid adoption of change. We have worked closely with other Universities in the development of a formal PF training curriculum and support a 14-week course conferring a nationally recognized PF certification. (54) For the current dissemination project, we plan to hire, train, and place PFs within each "intervention region". Each region will have an assigned PF. This staffing is supported by the program's philanthropic donation.

Pharmacy based community engagement:

This proposal includes several University of Minnesota College of Pharmacy based initiatives, such as the provision of live and web-based Continuing Education (CE) programs. Specifically, active learning-based CE modules are planned to raise pharmacist awareness, competency and action towards promoting appropriate aspirin use for primary prevention. Regional forums and targeted Pharmacy Association-based CE events will provide an opportunity to actively introduce campaign tools (including pocket cards, targeted website, qualifying eligibility tools, etc.) and provide a means to assess competency of attendees to understand the scientific data supporting the use of aspirin for primary prevention. They also provide an opportunity to assess practicing pharmacists' competency in providing effective, accurate advice regarding eligibility and use of aspirin for primary prevention. Faculty with the College of Pharmacy (Drs. Robert Straka and Jeannine Conway) have been collaborating with this initiative and are actively engaged with networks of pharmacists throughout the state, including a pilot project sponsored by the Minnesota Department of Health. This pilot project is being conducted in Marshall, Minnesota, and explores community pharmacist engagement on behalf of use of prescription cardiovascular risk reduction medications within the 'Million Hearts' campaign.

Evaluation

Population Surveys

The primary endpoint of this study, appropriate aspirin use for primary CVD prevention, will be collected by telephone survey in randomly selected age-eligible individuals. The group-randomized design includes 100 participants in each of 24 selected geographic areas for each survey. Individuals will be selected from commercially available lists of telephone numbers by zip codes. While cell phones are

increasingly used, hard line phones are more common in this age group. We anticipate that each survey will take three months to complete. In the pilot study, the University of Minnesota Center for Survey Research was able to maintain high participation rates and have staff available to perform this large survey. Based on our experience, the survey will take 8-12 minutes to administer. In addition to verbal consent, it will contain demographic questions, questions on aspirin use, cardiovascular disease status, physician contacts, risk factors, media exposure and other items that are relevant to understanding program effects. With these data, we will ascertain appropriate and inappropriate aspirin use. Appendix 9 is an example of a survey used in Hibbing.

From our and other population data, aspirin use in the target age range is increasing at approximately 1%/year. (Figure 1) This secular trend must be accounted in any analysis of program effects. We will survey 1200 additional age eligible adults in years 1, 3 and 5 living in adjacent Upper Midwest states (Iowa, North Dakota, South Dakota and Wisconsin) using the same telephone survey instrument as in Minnesota.

Process and Outcomes Measures

In order to assure that the health system intervention is effective, we have created a series of process measures that will serve as intermediate outcomes. These clinic-based measures include:

(i) The number and cumulative fraction of primary care health professionals who complete the aspirin primary prevention on-line training module;
(ii) The number of primary care patients, by clinic, that are identified as appropriate aspirin primary prevention;
(iii) The number of these candidates, by clinic, who are prescribed low-dose aspirin;
(iv) For clinics that use an EMR and the aspirin use data extraction, the rate of self-reported adherence to daily aspirin use.

In addition, we will monitor media exposure through our media contractor, Russell Herder, and data collected from the online site.

Morbidity Surveillance

The ultimate goal of this research and dissemination study is to improve cardiovascular disease and stroke morbidity in the Minnesota population. However, the primary endpoint is increased appropriate aspirin use.

We will monitor morbid events but recognize that multiple factors contribute to trends in heart attack and stroke rates or changes in bleeding-related hospitalizations.

In this study, we propose to monitor discharge diagnoses of myocardial infarction (ICD 410), ischemic and hemorrhagic stroke (ICD 430, 431, 433, 434, 436) and gastrointestinal bleeding (ICD 531-535). We recognize that there may be changes in the WHO ICD system. We will use accepted adjustment factors.

To collect these data, we will utilize our long-standing relationship with the Minnesota Hospital Association. This organization collects data from all hospitals in the state and has for several decades. The system is based on UB-04/A37 claims data. The inpatient data are grouped using the 3M (Minnesota Mining and Manufacturing, St. Paul, MN) Grouper and DRGs and APR DRGs are assigned. The data are comprehensive, including all hospitals and patient zip code identifiers of residences of admitted patients. This enables us to evaluate trends in different geographic areas of the state, as was done for the 1990-2011 period as shown in Figure 1.

<u>Economic Evaluation</u>

We will develop a model to assess the cost-effectiveness of the aspirin interventions using a societal perspective. We consider costs relating to the media campaign and interventions, individual behavior, medical care utilization, and productivity losses. Our primary output is the number of prevented AMIs among men 45 to 79 years of age and prevented strokes among women 55 to 79 years of age.

Using administrative data from budgets and contracts, we will measure annual costs associated with the mass media campaign (e.g., development and delivery of print ads, radio ads, and billboards), the online media intervention (e.g., development and maintenance of the website and related materials to promote it), and the professional education intervention (e.g., development and dissemination of EMR, face-to-face and online educational content) for each community. Because the campaign will encourage individuals to consult providers about aspirin use and begin taking aspirin daily if clinically recommended, cost estimates will also incorporate expenses for an office-based preventive care visit and aspirin.

Our primary data source for measuring medical care utilization and costs comes from the Minnesota Hospital Association's (MHA) uniform hospital discharge database. Using ICD-9-CM codes (see above), we will begin by identifying the subset of inpatient hospitalizations with a heart attack diagnosis among men 45-79 years of age and stroke diagnosis among women ages 55-79 in each community for the study

period.

Additionally, we will identify hospitalizations for major gastrointestinal bleeding. Zip code information contained on each patient's discharge record will facilitate community assignment.

To estimate costs, we will use total charges on the MHA discharge abstracts and apply cost-to-charge ratios to estimate condition-specific, transaction costs for use in the model. Lacking access to Minnesota-specific ambulatory care utilization and costs, we will estimate these items using alternative sources, such as the Medical Expenditure Panel Survey or Medicare Current Beneficiary Survey.

Productivity losses from onset of these conditions among working-age individuals (45-64 years) will be estimated with MEPS data on days lost due to the condition and wages. Given the multi-year study period, all measured costs will be inflation-adjusted and reported in constant dollars. Discounting methods will be employed also to account for differential timing of costs across the study period.

The number of prevented events will be computed by comparing total events in each of the intervention communities (online media only, physician education only, and online media and physician education) with the set of communities exposed only to the mass media campaign. With the cost and output information, we can compute the cost per prevented event associated with the ASA campaign and its respective interventions.

Analytic Methods

As previously stated, the programmatic hypotheses are:

Primary: The combined health system and media interventions will increase appropriate aspirin use for primary CVD prevention by absolute 15% in comparison to baseline against a secular trend of 1% per year. Secondary: Measurable differences will be detected between the intervention strategies.

a. Mass media alone (+5%).
b. Health system intervention (+10%).
c. The intervention effects will be sustained at year 5.

Approach. As rural areas will be less populated, weighting will be used to report descriptive statistics. Randomization will occur after the baseline surveys in each geographic pair. In a statistical design that randomizes socially intact groups, allowance must be made for similarity of behaviors within clusters arising from commonalities in selection, exposure, mutual interaction, or some combination of those factors (72); the amount of dependency of survey responses is the intraclass correlation (ICC). These commonalities are completely confounded within each cluster and so must be modeled as a random effect. (73) Because the clustering variance is necessarily estimated with only limited degrees of freedom (df), it is important to randomize sufficient clusters. (74-78) We will use analytic methods appropriate to the structure of the design and the data (61,64), namely the General Linear Mixed Model (79-84) for models assuming Gaussian errors, and the Generalized Linear Mixed Model (85,86) for categorical outcomes. Such models will be implemented using SAS procedures MIXED and GLIMMIX, Version 9.3. (87)

Primary Analysis. The design is a *member-cross-section* Group Randomized Trial (79) as respondents at baseline and at follow-up will not be restricted to be the same persons. We will use a mixed-model logistic regression analysis of 2 and 4-year follow-up aspirin use data, adjusting for baseline mean levels. In a preliminary step, the baseline aspirin use rate will be calculated for each geographic area, adjusting for respondent level covariates – age, gender, and race/ethnicity. At the 2 and 4-year follow-up surveys, the same covariates will be included on the record for each resident from the same geographic area measured. The primary analysis will regress the follow-up aspirin use values on the randomized study condition, resident covariates, and the area-specific and adjusted baseline aspirin use rate. Geographic area will be modeled as a random effect nested 'within study' condition. The model will be fit using SAS PROC GLIMMIX specifying a logit link and a binomial error. We will assess the null hypothesis of no joint intervention effect by testing the randomization condition (health system intervention versus media comparison) against the area-level (cluster) error term. Surveys will balance the numbers of men and women so as to allow the most sensitive analyses with gender strata.

Assumptions. This analysis assumes that there are two sources of random variation: geographic areas and residents. The observations are assumed independent conditional upon these random effects. There are additional assumptions inherent in regression adjustment for covariates (e.g., linearity, homogeneity); we will check those assumptions.

Advantages and Disadvantages. Advantages of this analysis are that it carries the nominal Type I error rate

across a variety of conditions found in GRTs (74-77); that it provides results that correspond to standard logistic regression analysis, except that the standard errors and df for fixed effects are constructed to reflect the extra variation and limited df due to the GRT design; that it often has good power compared to the alternatives (65,88,89); and that, the analysis is simple to conduct and to explain.

Alternate Approaches to the Analysis. We considered the GEE approach (90,91) which employs empirical sandwich estimation for standard errors and is asymptotically robust to misspecification of the random effects. This approach is particularly useful if there is some question about whether the assumptions for the random effects covariance matrix are appropriate, but we are satisfied in this case that our assumptions are reasonable. However, as a *sensitivity* analysis we will also compare results from using a model with the "empirical" method.

Power Analysis

Main Effects. We can adapt the methods from Murray (62) to provide this formula for the detectable difference that defines the main effect for either intervention in the mixed-model logistic regression analysis:

$$! = \sqrt{\frac{2\left(\sigma_y^2\left(1 - ICC_{m:g:c}\right)\Theta_m + m\sigma_y^2\left(ICC_{m:g:c}\right)\Theta_g\right)\left(t_{critical:\alpha/2} + t_{critical:\beta}\right)^2}{mg}}$$

The variance (σ^2_y) is estimated as p(1-p), where p is the prevalence rate for aspirin use at the follow-up among the members in the comparison clusters, projected at 0.3 based on Minnesota Heart Survey data. This variance is not particularly sensitive to the assumed level for levels between 20% and 80%. The Θ_m reflects any reduction in variance expected from regression adjustment for individual level covariates, whereas Θ_g applies to the baseline level of aspirin usage in the community. The Θ_m is not likely to be large, so we will be conservative and assume no benefit, that is, Θ_m=1. The community mean levels of aspirin use over the 3 years from baseline to follow-up may well be correlated (r=0.3 or larger; a correlation of 0.3 will provide a reduction in the community component of variance of about 10% (0.3^2); we will take Θ_g =0.09. Previous work suggests that ICCs are inversely related to the level of aggregation (92) and that ICCs in communities tend to be quite small, often less than 0.005. (92) To be conservative, we will use a value of 0.01. We propose 24 communities (g=12, df=22). In a member-cross-sectional GRT no allowance need be made for "loss-to-follow- up" as would occur in a member-cohort GRT. For 100 members per geographic area, a two-tailed Type 1 error rate of 5% will have 85% power for an absolute intervention effect of 8.1%, e.g., 30% vs. 38.1%; at 80% power the detectable difference would be 7.6%.

Secondary analyses - interactions. Gender specific analyses will have half the numbers of members for which the detectable difference will likely be closer to 10.0%. To test the contrast of the intervention effect in men versus women, the detectable difference between the gender specific intervention effects will be increased to 14.1%. Reducing power for these secondary analyses to a still acceptable 80%, these detectable differences are reduced to 9.4% and 13.1%, respectively.

Challenges

In a population based trial of dissemination as proposed here, there are challenges in design and analysis not faced in other research. We have considered many of these and pose responses:

Contamination: In the media intervention, the entire state will be exposed to the message. Similarly in the clinic interventions, there is potential for leaking of the intervention to control areas through the movement of health professionals, activation of patients and new clinic quality improvement activities. We control the geographic design and the export of our clinic-based programs. And the 'control areas' will receive the program in the second phase.

Telephone Survey: Population based telephone surveys have two major challenges: participation and cell phones. Our survey center has an excellent record with participation rates above 60% in random samples. We are calling hard line phones because cell phones are not always geographically linked and the recipient may be paying minute charges. In the target age range of this study, hard line use remains common.

Large Urban Areas: We have elected to exclude the Twin Cities and Rochester, Minnesota. The metropolitan area has clinical systems crossing all geographic boundaries and thus we cannot control contamination. Rochester, with the Mayo Clinic as the main industry, is unique and matching is not feasible. There are other areas in the state with >100,000 population we will randomize.

Secular Trends: Data from our work and that of others data finds aspirin increasingly used for primary prevention despite the lack of a coordinated campaign. Secular trends frequently undermine community-

based research. We propose to do surveys of the states adjacent to Minnesota to ascertain secular trends.