Preface:

David Lanier

Primary Care Practice-Based Research Comes of Age in the United States

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Multilevel Modeling and Practice-Based Research
Ann Fam Med 2005 3: S52-S60.
The enormous potential of practice-based research networks (PBRNs) to expand the knowledge base of primary care and to integrate research into practice (and practice into research) was recognized in the United States more than 25 years ago. Beginning with the development of early regional PBRNs in the late 1970s,1,2 the feasibility of conducting research in networks of primary care practices was quickly established. Throughout the 1980s and early 1990s, a steady stream of research reports from local, regional, and national practice networks then began appearing in the medical literature as the enterprise slowly grew and spread. Despite these successes, however, it was quite apparent that PBRNs as a group continued to face a number of challenges. Chief among these challenges was the absence of any systematic support for the growth and maturation of PBRNs. In its 1996 report on primary care, the Institute of Medicine viewed PBRNs as “a significant underpinning for studies in primary care” but noted that they were underfunded. One of the report’s recommendations was that “the Department of Health and Human Services provide adequate and stable … support to practice-based primary care research networks.”3

A few years later, the Agency for Healthcare Research and Quality (AHRQ) responded by releasing the first of a series of grant solicitations specifically targeting primary care PBRNs. From 2000 to 2004, AHRQ has made awards to primary care PBRNs totaling more than $8 million. Although the individual awards have been modest, the number and diversity of networks applying for these funds have been remarkable. The 45 networks that have to date received AHRQ funding for infrastructure support and pilot projects include among their members more than 10,000 primary care clinicians who care for more than 10 million Americans. In addition, in 2002 the agency invested in the establishment (through a contract with Indiana University and the National Opinion Research Center) of a PBRN Resource Center that has been given the task of assessing the developmental needs of AHRQ-funded networks and helping to meet these needs through educational, technical, and consultative services.

During the past decade, the number and diversity of identifiable primary care networks in the United States have increased dramatically. A brief communication published in 1994 reported that 28 primary care PBRNs were active at that time in North America.4 Most of these networks consisted predominantly, if not entirely, of family physician practices. By 2004, a national survey (conducted by the PBRN Resource Center) identified 111 networks in the United States that met certain established criteria for being an active primary care PBRN.5 The survey revealed that multiple types of practitioners, including pediatricians, general internists, and advanced practice nurses (in addition to family physicians), are represented in these networks, which are headquartered in 44 states. The data also indicated that a large number of these networks first emerged after 2000, when the seed money and other support offered to PBRNs by AHRQ first became available.

The clear challenge now facing the agency is how to continue supporting the growth and maturation of primary care PBRNs across the country in an era of projected federal budgetary limitations but with many more networks potentially needing our support. One approach has been to forge partnerships with other funding sources in both the private and the federal
At all stages of development, the article by Green et al. describes a wide range of topics and issues pertinent to networks. The National Institute of Health has supported individual PBRN projects, and the National Cancer Institute has been an AHRQ collaborator in funding network-based projects. For example, AHRQ and the National Cancer Institute are currently cosponsoring program announcements supporting investigations of PBRNs into methods of screening for colorectal cancer and methods of translating research into primary care practice.

Another way in which AHRQ hopes to continue promoting the growth and maturation of PBRNs is through the provision of regularly updated educational information to both emerging and established PBRNs. The articles included in this AHRQ-supported supplement to the *Annals of Family Medicine* were written with this educational goal in mind. To identify the most pertinent topics and content to be covered in the supplement, as well as the preferred author(s) for each article, AHRQ asked the supplement editor, Dr. Paul Nutting, to work with an advisory panel composed of a multidisciplinary group of individuals who are recognized leaders in network activities.* In addition, the PBRN Resource Center provided the editor with useful summary information derived from its assessment of the specific educational needs of PBRNs. It goes beyond the question of funding sources to describe the basic elements required by most or all PBRNs and how those requirements typically depend on the specific research mission of the network. Since releasing the first PBRN grant solicitation, AHRQ has been keenly interested in the development by PBRNs of systems for electronic data collection and aggregation. As Pace and Staton highlight, however, the benefits of these systems (such as improved data entry and integrity and easier data transfer) must be weighed against both their costs and the potential burden they place on research participants.

Because the relationships between primary care clinicians and their patients often span years or decades, PBRN researchers often have the opportunity to consider not only data from a single encounter, but also information collected longitudinally that spans entire episodes of care and describes the ongoing management of chronic health problems and the provision of health maintenance. The article by van Weel describes the benefits and the challenges of research that focuses on longitudinally collected data.

Even as data are collected, however, PBRN researchers need to be ever mindful of the potential effects of the Health Insurance Portability and Accountability Act (HIPAA) on the handling of patients' protected health information. The article by Pace et al. explores the ways in which HIPAA can affect research conducted in PBRNs. Closely related to concerns about HIPAA are important issues surrounding the review and approval of PBRN projects by institutional review boards (IRBs). Although the actual risks incurred by patients through participation in PBRN research are typically minimal, the process of seeking IRB approval can often be complicated and protracted for networks, which are sometimes required to have protocols reviewed by multiple IRBs. The article by Wolf et al. offers suggestions and options for networks to consider as they work with their local IRBs.

Finally, the article by Mold and Peterson on networks as quality improvement and learning collaboratives appears to challenge the traditional definition of PBRNs as research laboratories. AHRQ's work with PBRNs, however, has helped us recognize the potential of primary care networks to expand their purposes beyond traditional research to developing places of learning for clinicians. Equal to the goal of publishing research results should be the goal of nurturing an evidence-based culture in primary care. As Mold and Peterson indicate, engaging network practitioners in reflective inquiries can lead to practice improvement as well as to new researchable questions for the network.

The articles included in this supplement provide important information for those wanting to realize the benefits and the challenges of research that focuses on longitudinally collected data. As Pace and Staton point out, however, the benefits of these systems (such as improved data entry and integrity and easier data transfer) must be weighed against both their costs and the potential burden they place on research participants.

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*The advisory panel included Andrew Bindman, MD, MPH; Walter Calmbach, MD; Benjamin Crabtree, PhD; Margaret Grey, DrPH, CPNP; John Hickner, MD, MS; Wilson Pace, MD; Richard Wasserman, MD, MPH; and Barbara Yawn, MD, MS.
conduct high-quality research that expands the primary care knowledge base, and to improve the primary care of patients in the United States by ensuring that new knowledge is incorporated into actual practice.

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References


Infrastructure Requirements for Practice-Based Research Networks

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ABSTRACT

BACKGROUND The practice-based research network (PBRN) is the basic laboratory for primary care research. Although most PBRNs include some common elements, their infrastructures vary widely. We offer suggestions for developing and supporting infrastructures to enhance PBRN research success.

METHODS Information was compiled based on published articles, the PBRN Resource Center survey of 2003, our PBRN experiences, and discussions with directors and coordinators from other PBRNs.

RESULTS PBRN research ranges from observational studies, through intervention studies, clinical trials, and quality of care research, to large-scale practice change interventions. Basic infrastructure elements such as a membership roster, a board, a director, a coordinator, a news-sharing function, a means of addressing requirements of institutional review boards and the Health Insurance Portability and Accountability Act, and a network meeting must exist to support these initiatives. Desirable elements such as support staff, electronic medical records, multiuser databases, mentoring and development programs, mock study sections, and research training are costly and difficult to sustain through project grant funds. These infrastructure elements must be selected, configured, and sized according to the PBRN’s self-defined research mission. Annual infrastructure costs are estimated to range from $69,700 for a basic network to $287,600 for a moderately complex network.

CONCLUSIONS Well-designed and properly supported PBRN infrastructures can support a wide range of research of great direct value to patients and society. Increased and more consistent infrastructure support could generate an explosion of pragmatic, generalizable knowledge about currently understudied populations, settings, and health care problems.


INTRODUCTION

The infrastructures of practice-based research networks (PBRNs) differ widely, reflecting their varying origins and settings. Some were begun by physicians who had a strong desire to do research in community practice settings but had no set research program, whereas others were formed around a specific research agenda. The geographic scope of PBRNs ranges from national (eg, Pediatric Research in Office Settings, sponsored by the American Academy of Pediatrics, and the National Research Network sponsored by the American Academy of Family Physicians) to very local (eg, MetroNet, a 12-practice network in metropolitan Detroit sponsored by the Wayne State University Department of Family Medicine).

To date, very few data have been published about PBRN infrastructures. Basic survey data on the numbers and types of practices, clinician and patient demographics, geographic distribution, and studies completed or in progress are available for 86 of the 111 PBRNs identified by the PBRN Resource Center. Other authors have described medical records and busi-
ness systems information technology (IT) in practices in statewide family medicine and regional pediatric networks, but data on the research-support IT infrastructure of PBRNs themselves are lacking. Although case studies of single-network infrastructure development exist, at present, there is no comprehensive survey of PBRN infrastructure, much less any detailed analysis linking infrastructure elements to research productivity or efficiency.

The Agency for Healthcare Research and Quality (AHRQ) describes a set of basic infrastructure elements that must be in place for a PBRN to qualify for grant funding (eg, for RFA-HS-05-011 grants). These elements include the following:

- At least 15 ambulatory practices and/or 15 clinicians devoted to the primary care of patients
- A statement of the PBRN’s purpose and mission, including an ongoing commitment to research
- A director who is responsible for administrative, financial, and planning functions
- A support staff of at least 1 person reporting to the director
- A mechanism such as a community advisory board to solicit advice and feedback from the communities of patients served by the PBRN clinicians
- An organizational structure independent of any single study
- Communication processes such as regular newsletters, e-mails or listservs, conference calls, or face-to-face meetings

In the discussion that follows, we offer suggestions for configuring PBRN infrastructure. Our suggestions are based on our own experience and discussions with directors and coordinators of other PBRNs. We hope that the data linking structure to research productivity that we now lack will become available in the future and allow suggestions to be made on a more evidence-based footing.

**Common Infrastructure Elements**

Certain elements of infrastructure appear essential to support any successful PBRN: a director, a coordinator, a regular news-sharing function, some means of regular 2-way communication among the member practices, a membership roster, a provision for meetings, and an organized means of ensuring human subjects protection.

**Director**

The director is operationally responsible for the PBRN and is the individual accountable for management of the network. The director is typically a physician but may be a PhD researcher or another senior administrator. Training or experience in research is very desirable if not essential for this position.

The director is responsible for ensuring that proposed projects are evaluated in light of the network’s research focus and mission, resources, and other concurrent projects. (Networks differ in whether the actual decisions on prioritizing projects are made by the director, the governing board, a project review committee, or the membership as a committee of the whole.) The director need not be directly involved in active research within the network, but should know of all projects in the network. She or he often provides or arranges for mentorship and project development assistance for network members who have research questions and need help developing them. Outreach and recruitment of potential new network members, writing press releases, and giving talks at appropriate forums to reach existing and potential new members are also the director’s responsibility. If the network holds regular meetings, the director is usually responsible for leading those meetings. Finally, the director is responsible for daily administration, such as personnel and financial management.

It is essential not to underestimate the time commitment of the director. PBRNs require substantial in-person contact and hence make heavy demands on the director’s involvement. It is probably not practical to commit less than 0.20 full-time equivalents (FTEs) for even a small network, and 0.50 FTEs is more realistic for a network of any size. (In some networks, a team of investigators shares the personal contact function, reducing the time commitment required of the director.)

**Coordinator**

The PBRN coordinator is the key staff person responsible for the day-to-day operations of both the network and the projects within the network, and is critical to the success of a network. Although published data do not exist, we have developed a description of the successful coordinator from discussions at national PBRN workshops. Successful coordinators often have training and experience in both health care management and
INFRASTRUCTURE REQUIREMENTS FOR PBRNS

The coordinator position will ordinarily require at least 0.50 FTEs in even a modest-sized network. Larger networks will require more dedicated time and may divide the coordinator roles between 2 or more people.

One-Way Communication
The 1-way communication or news-sharing function of a PBRN is usually served by some combination of a newsletter and a Web site. The content of both will be quite similar. Newsletter intervals vary with activity; quarterly publication is a common choice. A Web site has the advantage of offering archival and reference information, but members must actively check it. Both forms of communication serve to celebrate successes, prepare for upcoming possible projects, reinforce contact information, and disseminate schedules. The value of a newsletter or Web site in making the PBRN known and attractive to potential new members should also be considered.

Two-Way Communication
The 2-way communication function of a PBRN is often supported by an e-mail listserv; that is, an e-mail service wherein listed members can both read and post comments. Discussion boards on a Web site are also possible, but require members to actively sign in to check on them. Two-way asynchronous communication is an effective means of developing ideas, managing active projects, and sharing news as well as collaborative feedback. It also serves the intangible but vital role of community-building, particularly in PBRNs that are geographically dispersed. The same listserv can also support the 1-way news-sharing function, if all or nearly all members of the network are subscribed.

Membership Roster
The roster may be anything from a simple list kept in the coordinator’s or director’s office to a full-scale multiuser database containing extensive descriptive information. A well-designed roster database will allow identification of practices for specific studies, support the mailing list for the newsletter and other communication tools, and provide information on the network (numbers, locations, and demographics of practices) to support grant applications.

Meetings
PBRNs generally have some form of regular meeting among members. In small networks, meetings may be as frequent as monthly, whereas in large or geographically dispersed networks, an annual assembly may be all that is practical. Larger meetings may serve more than the communication and community-building functions: they may include presentation of research results and
research proposals, training sessions for general methodologies or specific projects, and workshops on topics such as grant writing or manuscript preparation. Continuing medical education (CME) credit is often offered even at smaller meetings.

Geographically dispersed PBRNs with infrequent meetings may supplement their meeting schedule with regularly scheduled conference calls open to all members, hosted through commercial services or by hospitals or universities with telephone line resources. A new alternative, practical in only a minority of settings because of high-speed Internet requirements, is Web-based videoconferencing.

Board Function

All PBRNs require a board function, but how that function is served varies widely and depends to a great extent on whether the network functions primarily in a top-down, bottom-up, or whole-system fashion. Networks that are freestanding, nonprofit legal entities such as 501(c)(3) corporations, of course, have board structures dictated by their legal status. Some small unincorporated or institution-based networks function as a committee of the whole. Large institution-based networks generally require a formal board of directors, which may be appointed by sponsoring institutions or elected by the membership, or both. Patient representation on the board should be strongly considered, both to maintain patient-centered research values and because funding agencies are placing a great deal of emphasis on patient input at this organizational level. Alternatively, a PBRN may create a community or patient advisory board that reports to the governing board.

Human Subjects Protection Management

PBRN members and their office staffs must have training and certification in human subjects protection. At present, the required training programs vary widely and are often specific to host institutions or to funding agencies. A good starting point for an overview is the Bioethics Resources Web page of the National Institutes of Health (http://www.nih.gov/sigs/bioethics). PBRN infrastructure must include a means of knowing members’ progress toward certification and, ideally, support for helping them work through required material. Some PBRNs hold human subjects certification courses at their meetings, others give talks at members’ offices or hospitals, and some offer online training through their host institution.

PBRNs that are not entirely owned by or otherwise subsumed within a single health system will have to deal with multiple institutional review boards (IRBs), which typically vary widely in their procedures and requirements. A detailed database of IRB procedures and contact information, a collection of their forms, and at least 1 person experienced in working with them will be critical elements of infrastructure. This database must be well maintained, as IRB processes change relatively often.

Mission-Dependent Infrastructure Elements

For PBRNs intending to do only simple observational correlation studies, no formal infrastructure beyond the basics outlined above may be needed. PBRNs intending to carry out prospective cohort studies, clinical trials, or practice change interventions will need to consider dedicated research assistants (RAs), more sophisticated information management resources, training programs for members and their staffs, and formal linkages with the statistical and methodologic expertise of academic centers.

Research Assistants

The qualification of and funding for RAs vary with the local conditions of each network and the research mission(s) they undertake. Permanent RA positions that continue from one project to the next attract and retain more capable RAs, but must be supported financially during gaps between project funding streams. That support typically requires infrastructure support from a larger institution or a means to recover indirect costs or contractually set aside direct funds from grants to cover the gaps.

In some cases, practice staff rather than RAs collect study data. This substitution may necessitate financial support or other incentives for the practices. Using practice staff has 2 risks: research activities must compete with clinical demands for staff time and attention, and office staff may not be well or uniformly trained in research data collection. Both risks have implications for the generalizability of the patients recruited as well as the quality of the data obtained. The substitution of practice staff for RAs is nonetheless done successfully in many PBRNs and is advantageous particularly when geographic dispersion of practices is large, data collection procedures are straightforward, and data must be collected from many sites simultaneously. A brief, well-thought-out training program can allow gathering of high-quality data.

Information Technology Infrastructure

The elements of IT infrastructure can be considered in 2 categories, according to whether they function primarily at the practice level or at the network level. Here we will consider only those IT elements that directly relate to PBRN research, deferring practice business operations’ and general research issues such as statistics software to other authors.
At the practice level, electronic medical records (EMRs) can be helpful in PBRN research. They may be very helpful in providing practice demographics to support grant applications, identifying patients as candidates for studies, and providing data for retrospective chart review projects. Commercial EMRs are generally not designed for research, so proprietary systems do not even allow practices to access their own data for research without payment to the vendor. Choosing an EMR carefully, however, can maximize its usefulness in PBRNs. Practices contemplating the purchase of an EMR may wish to consider whether the data are structured in a manner that supports research queries, the ease of access for ad hoc queries, and whether data elements or forms can be added for specific research projects. At the network level, PBRNs may need to consider Web and file servers, shared databases, networking, and data collection equipment.

PBRNs desiring a Web site, listserv, or shared files require some form of server infrastructure. A wide variety of arrangements are possible, depending on local resources, expertise, and needs. A simple desktop computer with an always-on Internet connection may suffice; at the other extreme, the network may have space in a commercial or academic server-hosting operation. Regardless of the specific arrangements, three needs must be addressed: backup, security, and support. If any information of operational importance is kept on the server, a regular practice of backing up the data and server configuration should be in place; this practice protects against loss of data in unforeseen circumstances. Security needs will vary with information content: for example, a newsletter-type Web site is not sensitive, but a roster of practices with private office telephone numbers is. As a rule, PBRN Web sites themselves are not targets of hacking (illegal access), but any server is a target for takeover as a "zombie," including home computers connected to the Internet by a cable modem or a digital subscriber line (DSL). Security features should therefore be turned on and patches should be kept up to date. Support can be in the form of a person in the PBRN with suitable expertise, someone in an academic or organizational setting who supports the PBRN, or a commercially purchased support service, which may be included with space on an institutional server system.

As the size, scope, and sophistication of their research designs increase, PBRNs can find themselves hamstrung by what initially appeared to be the simple task of database design. Attention to relational design will save the growing PBRN a great deal of repeated work later. Multiuser databases (both for PBRN operations and for specific research projects) containing potentially sensitive information must be shared with, but restricted to, appropriate personnel, with careful attendance to security principles as described above. Off-the-shelf database systems designed to be user-friendly can present wide-open portals for unauthorized intrusion.

The PBRN whose research mission includes high-intensity activities such as clinical trials will require a means of highly secure communication. Each PBRN will arrive at its own solution based on its members' preferences and the technical expertise available to it, ranging from fax to virtual private networks (VPNs).

PBRNs with research missions that necessitate the collection of field data often equip research assistants with laptop computers. Infrastructure must then be in place to back up these computers frequently and reliably and to ensure that information contained on them remains secure in the event that one is lost or stolen.

Regulatory Compliance

PBRNs whose missions include health services research, quality improvement, or translation of research into practice will have to access medical records to measure physician practice patterns, and that access requires a system for ensuring compliance with the Health Insurance Portability and Accountability Act (HIPAA). HIPAA compliance can be maintained by negotiating a business agency agreement between the PBRN's host institution or nonprofit corporation and its member practices, wherein the PBRN is privileged to patient data for purposes of a quality audit or other business reason. An example of such an agreement is provided in Appendix, available online only as supplemental data at http://www.annfammed.org/cgi/content/full/3/suppl_1/55/DC1. Use of these patient data for research must still be specifically approved on a project-by-project basis, but a business agency agreement can at least credential a consistent set of PBRN research assistants to be able to abstract records across practices when a project receives IRB and HIPAA approval.

Research Consulting Expertise

PBRN projects usually require some level of statistical consultation and methodologic expertise. This expertise can be in the form of academic or private-sector researchers who are members, or nonmember experts who are retained by formal consulting arrangements. Specific forms of expertise are called for based on research mission. A PBRN planning clinical trials and one focused on epidemiology will have different needs. In most cases, these needs are addressed by an affiliation with an academic center.

PBRNs with research missions that require pursuing federal or equivalent grant funding will also benefit from holding regular mock study sections. A mock study section is a panel of 3 or more senior researchers with
national study section experience who review PBRN members’ grant applications before submission. The reviews must take place far enough before the submission deadlines to allow sufficient time for revisions before the application is due. They are typically conducted in a realistic study section format, but with the researcher(s) present in a “fly on the wall” fashion—listening and gaining insight into how the various components of their project may be received, but not permitted to explain or defend. That is, the application must stand on its own as it will in the actual study section. Written feedback is then provided to the researcher(s).

Closely related to the mock study section is mentoring and development. PBRN researchers have traditionally relied on their own initiative and had minimal resources, but as the pool of experienced researchers grows, it becomes more feasible for PBRNs to offer mentorship to new investigators. Mentorship is particularly useful to community practitioners whose important research ideas and perspectives can be thwarted by lack of training or experience in research methods.

Project-specific mentorship and guidance in development of a research project can be facilitated by a regular program of concept paper review (for an example and format, see http://www.ahrq.gov/about/cpcr/cpcr-conc.htm). A concept paper serves as a tool to refine a research idea and present it to potential collaborators and funding agencies. It also aids the PBRN staff and membership in assessing proposed projects for consistency with the PBRN’s mission and resources, as well as in ensuring that projects running concurrently avoid unnecessary interferences.

If a PBRN’s mission calls for studies requiring specific skills, such as clinical trials, the network will have to develop or arrange for research training for members. These programs will be specific to the research needs in question, and few useful generalizations can be offered, except that they will typically involve faculty from outside the PBRN. Programs may take place at a central meeting site or may convene at members’ practices. An offering of CME credit will improve acceptance and be appreciated by members.

### INFRASTRUCTURE COSTS

The costs of sustaining infrastructure have been perhaps the greatest single barrier to successful PBRN operations, from the earliest days of network research to the present. Funding agencies have long recognized that traditional bench and academic-center clinical research requires major infrastructure support to cover expenses ranging from building depreciation to the costs of retaining critically important trained staff during funding fluctuations, and have recognized that that support must be substantial. Those expectations are built into academic centers’ negotiated indirect rates. At the present time, however, few academic centers are willing to pass even a portion of these indirect rates to their PBRNs as they would to their clinical research centers, and funders are unaccustomed to thinking of PBRNs as the laboratories that they are, analogous to bench research edifices. As a result, PBRNs are often chronically underfinanced, operating on shoestring budgets and depending heavily on volunteer labor.

Costs of infrastructure vary with the research mission of the PBRN, but some commonalities across missions may be illustrative. Even a small network doing only simple epidemiology studies and other observational research (ie, a basic network) will require a half-time coordinator and a 0.20-time director, a laptop computer with a typical 3-year lifespan, a desktop computer, some technical support, a newsletter, and meeting, telephone, and fax expenses. A network with a larger membership, wider geographic dispersion, and a mission that includes intervention studies and externally funded research (ie, a moderate-complexity network) will require more director and coordinator time, 1 or more research assistants, travel expenses, secretarial staff with the skills to prepare competitive grant applications, and a sophisticated technologic infrastructure. Table 1 displays a simplified financial requirements for these 2 scenarios; the actual costs are only rough approximations of course and will vary

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<th>Table 1. Simplified Infrastructure Costs for Hypothetical Research Networks of Differing Complexities</th>
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<td><strong>Element</strong></td>
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<tr>
<td>Director (0.20, 0.50 FTE)</td>
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<td>Coordinator (0.50,1.00 FTE)</td>
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<td>Research assistants (2.00 FTE)</td>
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<td>Secretarial support (0.50 FTE)</td>
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FTE = full-time equivalent; NA = not applicable because the basic network does not have these elements.

INFRASTRUCTURE REQUIREMENTS FOR PBRNS
CONCLUSIONS

In this article, we have attempted to describe briefly the infrastructure requirements for divergent types of PBRNs and to describe a range of possible configurations. As yet, no inventory of PBRN infrastructure establishes clearly what the most common elements are. More importantly, there is no data-based way to determine what elements directly bear on the success of a PBRN. The work of Bland and Ruffin on success in a primary care practice-based research network. Inform Primary Care. 2004;12:11-18.

Fairly compensating members and their office personnel for their time and effort is the next major funding hurdle in infrastructure maintenance, and will require education of funders to recognize those costs as allowable direct expenses.

To read or post commentaries in response to this article, see it online at http://www.annfammed.org/cgi/content/full/3/Suppl_1/S5.

Key words: Primary health care; research support; community networks; program development; information management

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Primary Care Practice-Based Research Networks: Working at the Interface Between Research and Quality Improvement

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ABSTRACT

PURPOSE We wanted to describe the emerging role of primary care practice-based research, quality improvement (QI), and translation of research into practice (TRIP).

METHODS We gathered information from the published literature, discussions with PBRN leaders, case examples, and our own personal experience to describe a role for PBRNs that comfortably bridges the gap between research and QI, discovery and application, academicians and practitioners—a role that may lead to the establishment of true learning communities. We provide specific recommendations for network directors, network clinicians, and other potential stakeholders.

RESULTS PBRNs function at the interface between research and QI, an interface called TRIP by some members of the research community. In doing so, PBRNs are helping to clarify the difficulty of applying study findings to everyday care as an inappropriate disconnect between discovery and implementation, research and practice. Participatory models are emerging in which stakeholders agree on their goals; apply their collective knowledge, skills, and resources to accomplish these goals; and use research and QI methods when appropriate.

CONCLUSIONS PBRNs appear to be evolving from clinical laboratories into learning communities, proving grounds for generalizable solutions to clinical problems, and engines for improvement of primary care delivery systems.


INTRODUCTION

Primary care practice-based research networks (PBRNs) are challenging traditional distinctions between research and quality improvement (QI), emphasizing the importance of linking discovery and application, research and practice. These networks are finding that less translation is required to apply research to practice when clinicians are involved in deciding what to study, how to study it, and how to evaluate and present the results. Yet integration of research and practice is not easy because it often requires new kinds of relationships, conceptual frameworks, and even languages for clinicians, patients, researchers, academic institutions, and funding agencies.

In this article, we discuss these challenges and the various ways in which PBRNs are addressing them. We then propose that PBRNs are gradually evolving from clinical laboratories into collaborative learning communities that use both traditional and nontraditional methods to identify, disseminate, and integrate new knowledge to improve primary care processes and patient outcomes. The information on which we base our observations and conclusions was derived from publications, presentations, and informal conversations with individuals working in PBRNs in the United States.
States. Most of these networks are made up of small to moderate-sized, mixed-payer practices; however, we believe that the principles ought to apply to larger practices and managed care systems as well.

THE INTERSECTION OF RESEARCH AND QI

In medicine at least, research and QI have been considered fundamentally different activities. Research is defined as “a systematic search for facts,”1 whereas medical QI is defined as “an interdisciplinary process designed to raise the standards of the delivery of preventive, diagnostic, therapeutic, and rehabilitative measures in order to maintain, restore, and improve health outcomes of individuals and populations.”2 The primary emphasis of research is thus on discovery, and the primary emphasis of QI is on application. Some other distinctions have been made between research and QI in the medical and nursing literature (Table 1).3-15

Academics often approach research as if it were a goal. They speak about the importance of doing research as opposed to using research methods to answer a question or solve a problem to improve outcomes. This approach is understandable because success in academia is generally measured by numbers of grants, publications, and presentations, not by improved clinical processes or population health. The focus of primary care clinicians, on the other hand, is on outcomes. They are interested in solutions to everyday challenges, and their experience with research suggests that it rarely provides such solutions. The questions that are addressed in studies too often seem reductionistic, esoteric, uninteresting, and disconnected from the realities of patient care. Results may take years to become available for everyday use.

Successful PBRNs have recognized that, for researchers and clinicians to choose to work together for an extended period of time, they must focus on outcomes that are relevant to clinical practice, that is, solutions to the challenges that clinicians and their patients face on a frequent basis. Not surprisingly, the methods required include both discovery (research) and application (QI). In the corporate world, this combination is called research and development. The key question for a new or emerging PBRN to ask is, “What can we accomplish more effectively or efficiently by working together in a practice-based network?”

Organizations involved in QI have discovered the benefits of extending their work beyond individual practices. Although these QI organizations still assess individual clinician or practice performance, they also compare performance across clinicians and practices, creating performance benchmarks. Within the bounds of confidentiality, they use these benchmarks to motivate practices or to create competition, and they share the information they have learned from more successful practices with less successful ones.16-20

Many QI organizations are also using a method pioneered by the Institute for Healthcare Improvement called Breakthrough Series Collaboratives.21-32 Collaboratives generally include 10 to 20 unrelated clinical practice teams working both independently and collaboratively for a period of 6 to 8 months to improve performance in a predetermined area (eg, management of patients with diabetes). Under the guidance of local and national experts, team members study, test, and implement the latest available knowledge to produce rapid improvements in performance. The rapid cycle method of QI—Plan-Do-Study-Act—is taught and encouraged. Individual successes and failures (the discovery component) are shared via listservs and during periodic conference calls and meetings, and improvement guides (the application component) are developed and disseminated based on lessons learned within the collaborative and from other collaboratives. Clearly, these activities include both discovery and application, research and QI.

Several PBRNs (eg, the Oklahoma Physicians Resource/Research Network [OKPRN], the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Research</th>
<th>Quality Improvement</th>
</tr>
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<tbody>
<tr>
<td>Intent</td>
<td>Discovery</td>
<td>Application</td>
</tr>
<tr>
<td>Impetus driven by</td>
<td>Current state of knowledge</td>
<td>Needs of end users</td>
</tr>
<tr>
<td>Circumstance</td>
<td>Optional</td>
<td>Often required</td>
</tr>
<tr>
<td>Foundation</td>
<td>Theory-driven</td>
<td>Application-driven</td>
</tr>
<tr>
<td>Philosophy</td>
<td>Naturalism</td>
<td>Pragmatism</td>
</tr>
<tr>
<td>Conduct</td>
<td>Preplanned</td>
<td>Iterative</td>
</tr>
<tr>
<td>Consent</td>
<td>Required</td>
<td>Implied</td>
</tr>
<tr>
<td>Source of data</td>
<td>Multiple organizations</td>
<td>Single organization</td>
</tr>
<tr>
<td>Audience</td>
<td>Multiple organizations</td>
<td>Single organization</td>
</tr>
<tr>
<td>Deviation from usual practice</td>
<td>Significant</td>
<td>Minimal</td>
</tr>
<tr>
<td>Unit of analysis</td>
<td>Patient or clinician</td>
<td>Clinician or practice</td>
</tr>
<tr>
<td>Outcome measures</td>
<td>Study specific/additional</td>
<td>Routinely collected data</td>
</tr>
<tr>
<td>Evaluation criteria</td>
<td>Scientific rigor</td>
<td>Process validity</td>
</tr>
<tr>
<td>Benefit to participants</td>
<td>Little direct benefit to most participants</td>
<td>Direct benefit to most participants</td>
</tr>
<tr>
<td>Level of risk/burden to participants</td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td>Timeline</td>
<td>Years</td>
<td>Weeks or months</td>
</tr>
</tbody>
</table>

Table 1. Traditional Distinctions Between Research and Quality Improvement

In medicine at least, research and QI have been considered fundamentally different activities. Research is defined as “a systematic search for facts,”1 whereas medical QI is defined as “an interdisciplinary process designed to raise the standards of the delivery of preventive, diagnostic, therapeutic, and rehabilitative measures in order to maintain, restore, and improve health outcomes of individuals and populations.”2 The primary emphasis of research is thus on discovery, and the primary emphasis of QI is on application. Some other distinctions have been made between research and QI in the medical and nursing literature (Table 1).3-15

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Several PBRNs (eg, the Oklahoma Physicians Resource/Research Network [OKPRN], the
TRANSLATION OF RESEARCH INTO PRACTICE

There has been increasing concern in the last few years about the failure of research findings to rapidly affect clinical practice.\(^{34-41}\) This failure has highlighted the difficulties clinicians encounter when trying to implement new approaches in their practices and the relative ineffectiveness of traditional methods such as continuing medical education and journal publications for disseminating new medical information.\(^{52-50}\) Using the results of a number of published studies, Balas and Boren\(^ {51}\) estimated that it takes an average of 17 years to turn 14% of original research findings into changes in care that benefit patients.

Clinicians have responded that much of the new knowledge published in journals is not directly applicable to practice. They also point out that clinical practice is complex, and that even potentially relevant research findings must be adapted to fit fiscal realities, individual practice styles and configurations, and unique patient populations and communities.\(^ {52-54}\) These concerns have led to a perceived need for more relevant research and for better ways to translate research into practice (TRIP).\(^ {55}\)

Primary care PBRNs are well positioned to accomplish both because they include parties on both sides of the translational gap, researchers and clinicians. In fact, PBRNs are not only addressing these issues, they are also reframing them. For example, an assumption of TRIP is that research flows from the bench (laboratory) to the clinic, an assumption challenged by members of PBRNs, who suggest that it is as important to put practice into research as it is to put research into practice. In theory, when clinicians are involved in decisions regarding what to study, how to study it, and how to analyze and frame the data, they are more likely to find the results to be both useful and usable. Research carried out in practice settings should be more relevant and generalizable. When clinicians actually participate in a research project, furthermore, they are probably more likely to use the results. To the extent that this phenomenon is due to the Hawthorne effect, it would be viewed as contamination in classical research, but in practice-based research, it is viewed as a benefit.

The National Institutes of Health and the Agency for Healthcare Research and Quality are now funding research that informs the translational process.\(^ {56-58}\) Their question seems to be, “How can we get physicians to do the things that we know, from previous research, work?” PBRNs are certainly participating in this effort, but they are finding the question to be more complicated. For example, practice guidelines and quality standards, based on research, rarely take into account comorbidities, financial barriers, and patient

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Example: The Colorado Ambulatory Research Network

The Colorado Ambulatory Research Network (CaReNet) and the affiliated High Plains Research Network improve practice by routinely capturing and analyzing patient safety errors. Error patterns are compared with statewide malpractice claims data and presented to a clinical steering committee, which identifies areas of greatest concern or opportunity for improvement. Through direct observation in participating practices, practice research coordinators (PRCs) construct maps of the relevant processes. Each practice then appoints members to a learning group made up of representatives from all parts of the practices. These learning groups analyze and discuss the errors data and the process maps, and develop theories and strategies called practice process improvement reports. Researchers and PRCs then turn these reports into planned intervention and evaluation cycles. Their discoveries and successful interventions are presented at national meetings and published in peer-reviewed journals.\(^ {51}\)

Recommendations

For Network Directors

• When talking with academic colleagues or preparing grant applications, use the term research instead of the term quality improvement. When talking with clinicians, however, note that in most cases “research” is not a very useful word.

• Work collaboratively with clinician members to solve problems and achieve objectives that immediately improve practice or help patients. Use traditional research methods when appropriate to achieve those ends, and use other methods when they work better than traditional ones.

• Look for opportunities to develop relationships with QI organizations and other organizations interested in improving primary care practice and patient outcomes.

For PBRN Clinician Members

• Do not let the academicians take over your network. Insist on a strategic plan that makes sense to you and your patients.

• Make sure that the work is not just about getting grants and publishing papers. Insist that the results be framed so that they are clinically useful.
priorities, and very few of them have been adequately field-tested. Information is also emerging about the complexities of primary care practices and the lack of appropriate systems and resources necessary to make meaningful changes. Implementation of new research findings often requires major changes in office systems, including changes in staffing and staff responsibilities, and patient scheduling and flow patterns, as well as installation of new technologies, which can often only be accomplished with outside assistance.

Example: Improving Diabetes Care by Primary Care Translation
MAFPRN has been using technology to help drive research into sustainable clinical practice. The IMPACT study is a randomized controlled trial of a highly developed, multifaceted diabetes intervention in 24 primary care clinics. The intervention begins by evaluating the organizational structures of primary care offices and identifying existing barriers. A set of 9 intervention components is then introduced to correct existing deficiencies at each clinic. Key features include targeting of high-risk patients, a patient reminder system for routine visits, both generic and patient-specific physician reminders, a diabetes registry, a networked reporting system, and physician education. Implementation of the intervention is facilitated by a local diabetes intervention team assisted by a site coordinator and a local physician champion.

Recommendations
For Network Directors
• Do not hesitate to question basic assumptions about translation and the generation and flow of information. Consider doing research that challenges these assumptions, and that both clarifies and reduces the gaps between research and practice.
• Encourage and support attendance by clinicians at national research meetings, and advocate for inclusion of clinicians on review panels and as peer reviewers for journals.

For PBRN Clinician Members
• Insist that clinicians play a major role in setting the agenda for PBRN activities, in planning specific projects, and in deciding how to frame and disseminate the results.
• Seize opportunities that arise to attend national research meetings or to serve on review boards or as a peer reviewer for a journal.

PARTICIPATORY RESEARCH IN PBRNS
In an effort to address TRIP, numerous PBRNs have tried to involve clinicians in as many steps of the research process as possible. A diagram constructed at a primary care methods conference in 2000 illustrates this concept (Figure 1). Some PBRNs (e.g., the University of California, San Francisco–Stanford Research Network and OKPRN) have developed research training programs for clinicians to enhance their ability to participate in all phases of the research process.

When a multidisciplinary group can focus on common goals, however, it is not usually necessary or desirable for everyone to participate in every step. The term community-based participatory research has been used to describe research conducted collaboratively with and within communities, in which the goals are improved community-based outcomes, and all phases of the project are approved by a committee that includes stakeholders and methodologists. The principles of this research approach can be found in a position paper endorsed by the North American Primary Care Research Group. The key features are a strong foundation of understanding, respect, and trust among the participating entities; a set of mutually agreed-upon goals; and a governance structure and rules of conduct that ensure that the process will remain collaborative from goal generation to implementation and dissemination of results.

The community-based participatory research model seems well suited to PBRNs, in which the “community” could include clinicians, their office staff, their patients, various local health-related organizations, or combinations thereof. Major obstacles to progress in this area have been the time and funding required to establish and maintain the foundational relationships. In a par-

Figure 1. Diagram of practice-based research involving clinicians in research steps.

<table>
<thead>
<tr>
<th>Practice-based Research</th>
<th>Identify gap</th>
<th>Search for answers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implement results</td>
<td>a.</td>
<td>b.</td>
</tr>
<tr>
<td>Generate study questions</td>
<td>c.</td>
<td>d.</td>
</tr>
<tr>
<td>Design study</td>
<td>e.</td>
<td>f.</td>
</tr>
<tr>
<td>Analyze data</td>
<td>g.</td>
<td></td>
</tr>
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</table>

Note: Diagram constructed by Nutting at the Primary Care Methods Conference, San Antonio, Texas, 2000.
ticipatory process, all participants contribute to and gain from the process, but the focus is always on the community as a whole. This approach requires a major attitudinal shift for many academicians, because in this model, researchers contribute methodologic expertise but generally have less influence over the goals than do other partners, and implementation of the results takes precedence over publications and academic accolades, although the latter are an important by-product.

Example: The Dartmouth–Northern New England Primary Care Cooperative Research Network

During a New England blizzard 20 years ago, a heated debate took place among clinicians from the Dartmouth–Northern New England Primary Care Cooperative Research Network (the COOP). The topic: do doctors really know what matters to their patients? As a result of that discussion, the clinicians carried out a study subsequently published in the *Journal of the American Medical Association* in 1983. The findings showed that, in fact, doctors and nurses are frequently unaware of what matters most to their patients.

For more than 30 years, the COOP has functioned as a voluntary network of independent primary care clinicians in New Hampshire, Maine, and Vermont. Clinician members meet regularly to advise the COOP staff, prioritize research activities, and determine organizational policies. Many of the COOP’s members are in small towns and rural areas that lack a large clinician community or opportunities to discuss clinical innovations and other subjects of interest to physicians and nurses. As a forum for intellectual exchange, the COOP has enabled clinicians to serve as sources of information for each other, which has affected clinical practice.

Over the years, the COOP has also successfully competed for millions of dollars in grants from the National Institutes of Health and private foundations, and has published more than 50 peer-reviewed articles, all focused on increasing the ability of clinicians to understand and respond to patient needs and concerns. As a result of its 1983 study, the COOP membership elected a governing board of practicing clinicians to provide guidance to the Dartmouth Medical School’s Department of Community and Family Medicine. During the past 5 years, the COOP has also worked closely with the Institute for Healthcare Improvement to improve interactions between patients and clinicians.

Recommendations

For Network Directors

- Read about community-based participatory research, and consider adapting the principles within your PBRN.

- Develop an organizational structure that includes all relevant stakeholders, and a process that focuses on common goals and objectives.

- Recognize and make optimal use of the skills and resources of all participants.

For PBRN Clinician Members

- Recognize that although academicians have certain important skills and resources, these assets are insufficient. Your skills and resources and those of other potential partners are at least as important to the success of the network and its work.

PBRNS AS PROVING GROUNDS

Some have proposed that professional associations should encourage all of their members to become involved in PBRNs to accelerate the process of discovery and dissemination of new information. Others have advocated limiting membership in PBRNs to highly committed clinicians who are willing to invest extra time and effort to discover and test ways to improve care, relying on traditional strategies (eg, publications and presentations) and affiliations with other organizations (eg, QI organizations, state health departments, professional associations) to disseminate the results.

Some QI organizations view the networks as proving grounds—sources of good ideas and effective solutions to important clinical and administrative challenges. The QI organizations help fund these efforts and then disseminate the findings. Similar relationships have been developed with other governmental and private organizations. For example, a state department of health has collaborated with a PBRN to develop ways to encourage greater use of its immunization registry. The method will be developed and tested in the network before its dissemination throughout the rest of the state. A private software development company might establish a contractual relationship with a PBRN to learn what clinicians need, then develop and test products in the network, hoping to eventually sell them outside of the network. The network could then earn a small share of the profits.

Example: The Practice Partner Research Network

The Practice Partner Research Network (PPRNet) is a network of primary care practices that all use the same Electronic Health Record—Practice Partner (Physicians Microsystems, Inc, Seattle, Wash). Their approach to research, QI, and collaborative learning has 3 major components: practice reports, site visits, and network meetings. Practice reports show historical and current practice-level adherence with clinical guidelines, as well as with PPRNet and national benchmarks. Site visits by
a physician with expertise in the practice guidelines, practice-based QI, and the Practice Partner Electronic Health Record occur 2 to 4 times annually. These visits provide an opportunity for academic detailing, assistance with QI efforts, and additional Electronic Health Record training. At annual network meetings, clinicians and staff members share best practice approaches for improvement. Sites can also request and receive between-visit e-mail and telephone support from the project team.

Lessons learned in PPRNet can be disseminated by Physicians Microsystems, Inc, to its other users and incorporated into software updates and improvements in training. The company can also point to its affiliation with the Medical University of South Carolina and PPRNet as evidence of innovation and stability, and to potential membership in PPRNet as an advantage of purchasing their software.

**Recommendations**

For Network Directors

- Be sure that the organization of your network is aligned with its mission. Consider the advantages of a small, highly motivated membership in terms of efficiency and effectiveness, but also its limitations in regard to the generalizability and dissemination of project findings.
- Clarify the purpose of your network in such a way that potential stakeholders and funding agencies can understand how they can collaborate and contribute.

**PBRNS AS LEARNING COMMUNITIES**

The assumption that research flows in only one direction leads to the belief that all knowledge flows in that same direction. As a result, the knowledge acquired by primary care practitioners while doing their jobs has been discounted and, therefore, has largely gone untapped. Most clinicians never publish papers or give presentations at meetings. Within the QI community, there is a recognition that true learning builds from microsystems to organizations. It is at the front line, where patients, clinicians, and information meet, that learning begins. A leader or organization that attempts to improve quality of care from the top down may have some effect, but it is unlikely to be large or sustainable.

PBRNs are learning to mine the wisdom of practitioners to more effectively and efficiently address common clinical and administrative challenges. The methods used include interviews, surveys, and direct observation. Knowledge exchange also occurs on listservs, at project development meetings and network convocations, through newsletters, and via practice facilitators. Newer methods, such as best practices research, allow researchers to systematically identify, characterize, and disseminate new knowledge and applications derived from frontline clinical and administrative microsystems.

DuFour and Eaker and others state that there are 6 characteristics of a professional learning community: (1) a shared mission and values, (2) collective inquiry, (3) collaborative teams, (4) an action orientation including experimentation, (5) continuous improvement, and (6) a results orientation. As PBRNs evolve, they appear to be incorporating many of these principles.

**Example: The Oklahoma Physicians Resource/Research Network**

OKPRN is organized geographically into pods of practices, and each pod has a practice enhancement assistant (Figure 2). These assistants identify and exchange ideas, methods, questions, and challenges between practices within their pod and, through the central office, to the rest of the network; facilitate QI; and assist practices to participate in network-wide projects. Practice enhancement assistants also help practices apply the information gained from network research projects. In addition, collaborative learning occurs via an active member listserv, a Web site, a biennial newsletter, practice visits by the network director, and 2 convocations per year.
Researchers affiliated with this network have developed a method called best practices research to answer questions of the form, “What is the best way to do ———?” This method involves dividing the process being studied into its individual steps or components, establishing criteria for what constitutes best practice for each step, identifying exemplars from the network for each step using practice audits, combining the methods used by exemplars into a combined best method, and then testing the combined method in other network practices. The advantages of tapping into the wisdom of practitioners in this way include efficiency (an important requirement in practice-based research), feasibility, and the fact that solutions, or at least their components, have already been field-tested. Examples of processes studied to date include management of laboratory test results, management of prescription refills, care of diabetic patients, and delivery of adult immunizations.

Recommendations
For Network Directors

- Build into your network as many ways as possible for network members to learn from each other.
- Consider developing ways to systematically capture and disseminate good ideas and successful approaches.
- Read about professional learning communities and learning organizations, and incorporate the concepts into your network.

VALUE AND SUSTAINABILITY OF PBRNS

If an organization produces sufficient value for its members, the members will make sure that the organization survives. It is therefore critical that PBRNs understand what their members value. Likewise, if an organization produces sufficient value for others, they will support it. Financial support can almost always be found to do things that are worthwhile. It is therefore important to include potential beneficiaries in organizational decision making. PBRN advisory boards often include clinicians, office staff, patients, academicians, public health officials, and representatives of professional associations, QI organizations, insurance carriers, and private industry. Funding sources include both grants and contracts from a variety of sources. Some PBRNs are also considering membership dues and charitable contributions programs.

PBRNs are extremely frugal and efficient organizations, but they do require predictable financial support for infrastructure and additional project-specific revenues. Most have depended heavily on in-kind support from academic medical centers. Faculty and staff resources can be devoted to PBRN activities because these activities lead to grants, contracts, publications, presentations, tenure, and promotion for faculty and various intangible benefits to the academic medical center (eg, community goodwill, patient referrals, legislative support). This relationship can, however, result in an overemphasis on traditional academic values (eg, publications, grants), leading back to research as the goal and an underappreciation of the values and needs of PBRN members and other critical partners.

Academic faculty and staff are critical components of effective networks. Busy clinicians have little time and insufficient skills to write grant applications, design studies, and direct most projects, but academicians must learn to become contributors to a collaborative effort rather than the sole drivers of the effort. Principal investigators must be willing to subjugate their own research agendas to the needs and interests of the group. Successful networks have been able to find researchers willing to do this, but in many institutions, it may be necessary to train researchers and administrators.

Recommendations
For Network Directors

- Identify researchers who are more interested in improving primary care practice than they are in studying a single topic area, or identify a large enough cadre of researchers to cover the methodologic needs of the network.
- Develop training programs (eg, workshops, seminars, mini-fellowships) wherein researchers interested in working with your network can be trained.
- Identify organizations and funding agencies that share your network's mission and goals. Include them on your advisory board, and keep them apprised of your activities and accomplishments. Encourage network members to serve on these organizations' and agencies' advisory boards as well.
- Consider instituting membership dues as a way to generate funds for infrastructure and to increase commitment to the network.
- Approach your academic medical center or hospital's development office for help in identifying potential charitable contributions. Point out to the medical center the value of a PBRN including, but not limited to, community goodwill, subspecialty referrals, and grants and contracts.

For PBRN Clinician Members

- Begin talking about the network with your patients. Ask some of them about their interest in making a financial contribution.
- Approach retired colleagues and others who might have an interest in network activities.
CONCLUSIONS

Primary care PBRNs appear to be evolving into collaborative learning organizations that use techniques borrowed from QI and research, and developing new methods of their own. These networks are bridging traditional gaps between town and gown, public and private, and research and QI. Technologic advances have increased the ease of communication, collaboration, and data sharing, which may substantially alter existing models of research and practice. Barriers that have traditionally separated the researcher from the practitioner are disappearing. Whether PBRNs will become the engines of innovation and improvement in the delivery of primary health care will depend on the ability and the commitment of the critical partners and stakeholders to work together toward worthwhile goals.

To read or post commentaries in response to this article, see it online at http://www.annfammed.org/cgi/content/full/3/Suppl_1/S1512.

Key words: Primary health care; quality improvement; practice-based research network; practice-based research; quality of health care

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Electronic Data Collection Options for Practice-Based Research Networks

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ABSTRACT

PURPOSE We wanted to describe the potential benefits and problems associated with selected electronic methods of collecting data within practice-based research networks (PBRNs).

METHODS We considered a literature review, discussions with PBRN researchers, industry information, and personal experience. This article presents examples of selected PBRNs’ use of electronic data collection.

RESULTS Collecting research data in the geographically dispersed PBRN environment requires considerable coordination to ensure completeness, accuracy, and timely transmission of the data, as well as a limited burden on the participants. Electronic data collection, particularly at the point of care, offers some potential solutions. Electronic systems allow use of transparent decision algorithms and improved data entry and data integrity. These systems may improve data transfer to the central office as well as tracking systems for monitoring study progress. PBRNs have available to them a wide variety of electronic data collection options, including notebook computers, tablet PCs, personal digital assistants (PDAs), and browser-based systems that operate independent of or over the Internet. Tablet PCs appear particularly advantageous for direct patient data collection in an office environment. PDAs work well for collecting defined data elements at the point of care. Internet-based systems work well for data collection that can be completed after the patient visit, as most primary care offices do not support Internet connectivity in examination rooms.

CONCLUSIONS When planning to collect data electronically, it is important to match the electronic data collection method to the study design. Focusing an inappropriate electronic data collection method onto users can interfere with accurate data gathering and may also anger PBRN members.


INTRODUCTION

Practice-based research networks (PBRNs) strive to collect high-quality data in clinical environments in geographically dispersed institutions. A number of PBRN researchers have turned to electronic methods of data collection to improve the quality of data and the collection process while decreasing cost and eliminating secondary data entry. Given the required investment in hardware, software, and training, PBRN researchers must carefully consider both the pros and cons of adopting electronic data collection methods. This article explores the potential benefits and limitations of electronic data collection within PBRNs. Table 1 lists the tools we refer to and the terms we use.

The information presented here is derived mainly from our own experiences and discussions with leaders of PBRNs in the United States. We also examined a convenience sample of literature about PBRN studies using electronic data collection methods, that is, articles we could identify on PBRN studies in which the data were collected by some electronic means.
Table 1. Electronic Data Collection Tools and Terms

<table>
<thead>
<tr>
<th>Ease of Implementation</th>
<th>Technology</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easier to implement</td>
<td>Notebook computer</td>
<td>A portable computer that is operated by using a keyboard. Traditional notebook computers now overlap with tablet PCs (described below). A tablet PC can be operated as a notebook. Most notebook computers do not support touch screens and cannot be configured so that the screen is accessible when flat against the body of the computer</td>
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<tr>
<td></td>
<td>Thick client</td>
<td>A system that operates with part of the software loaded on the workstation and that is continuously in contact with the data repository</td>
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<td></td>
<td>Internet-based system</td>
<td>A system run over the open Internet (also referred to as the Web or World Wide Web) as opposed to over a dedicated LAN or WAN. Security measures can be applied to the data transferred between 2 points in the system (such as with encryption or by creating a VPN) to markedly improve the safety of data passed across these systems</td>
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<td></td>
<td>Browser-based system</td>
<td>A system wherein the screens are loaded into the workstation’s Internet browser as needed from a central server. Information is returned to the server at a later time (seconds, minutes, or days later, depending on how the system is used). The workstation and the server only communicate with each other through “requests” from the workstation (ie, clicking the Submit button). These systems are considered “stateless” in that they only intermittently connect the server and the workstation</td>
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<td></td>
<td>PDA</td>
<td>A small handheld computer that can be easily carried, that typically has an instant-on feature, and that provides rapid access to data, software, and data input systems. These computers typically operate independent of a network or the Internet, although wireless connectivity is becoming more common. The most common operating systems within the United States are Palm OS (PalmSource, Sunnyvale, Calif) and Pocket PC (Microsoft Corp, Redmond, Wash)</td>
</tr>
<tr>
<td>More difficult to</td>
<td>Tablet PC</td>
<td>A computer that, like a PDA, is operated by using a touch screen but that has a larger screen and often greater computer power. Currently, tablet PCs—with or without built-in keyboards—operate on a full version of Microsoft’s Windows XP and may contain relatively large hard drives. These computers are often operated over a wireless network, but may operate independently. Tablet PCs are configured so that the screen may be used and viewed while flat against the body of the computer, much like a tablet of paper</td>
</tr>
</tbody>
</table>

LAN = local area network; WAN = wide-area network; VPN = virtual private network; PDA = personal digital assistant.

WHY COLLECT DATA ELECTRONICALLY?

Primary care PBRNs have traditionally asked practicing clinicians and office staff to collect research data while seeing patients.1-4 The Ambulatory Sentinel Practice Network (ASPN) popularized the “card study,” in which clinicians carried a small card with them and completed a short set of questions for selected patients. Variations of this method have been widely used by PBRNs.5-9 The card study moves data collection into the office environment, yet it presents considerable challenges to ensuring data integrity. Missing or hard-to-interpret responses are common and can be labor-intensive to correct. Cross-sectional studies of this type, furthermore, can answer only a limited set of research questions. Improvements in data collection methods that support expanded research designs are crucial for PBRNs to become the laboratory that drives primary care practice.

PBRNs have experimented with electronic data collection for a number of years. The International Primary Care Network (IPCN) collected data on otitis media in 4 countries from 131 family physicians and general practitioners using early personal data assistants (PDAs).10 The technology was new and connectivity proved difficult11; nonetheless, the future of handheld data collection looked promising. The Dartmouth Primary Care Cooperative Research Network (Dartmouth COOP) developed and operates a patient Web site that collects information for community, practice, personal, and research use.12,13 Steve Ornstein of the Practice Partners Network and Henk Lamberts of the University of Amsterdam and the Transhis project established groups of practices that use a single electronic health record (EHR).14 Lamberts not only extracted data from the EHR for research purposes, but added project-specific research questions to the EHR for periods of time. The introduction of enhanced technology during the past decade has heightened researchers’ expectations of electronic data collection.

ELECTRONIC DATA COLLECTION OPTIONS

The directors and staff of PBRNs have available to them an array of options for electronically collecting data. Various methods of electronic data collection have strengths and weaknesses; therefore, it is important to match the method to the study design. PBRN staff should be familiar with the full gamut of options available. It is also important to not force inappropriate technology on a network or study design. If the appropriate electronic method is not available, a PBRN should revert to paper methods instead of pushing an inappropriate technology for the study. To understand what may be an appropriate electronic data collection method, one must understand the benefits and limitations of the available technologies. In this sections, we...
describe a number of technologies that could be used for data collection across a PBRN.

**Working With Existing Data Sources**
The search by PBRNs for a so-called painless or free means of collecting additional data to supplement specific point-of-care data has typically centered on mining existing data. Adding demographic, diagnostic, or service data to information collected at the point of care can reduce the burden on clinicians and practices, and enhance available information. Collecting these data typically requires patient consent (a difficult, time-consuming task for which most clinicians do not have the time and are not trained to perform). With the advent of the Health Insurance Portability and Accountability Act (HIPAA), the use of existing data to support, enrich, or replace specific research-driven data collection activities has become more difficult. Models that develop business partner agreements between the practice and the PBRN offer hope in this regard.

Full EHRs offer promise for obtaining electronic data with less effort than that required by traditional paper methods. Unfortunately, data in EHRs are rarely collected according to a study protocol and are highly variable in scope and meaning, even when templates are used. Most EHRs, furthermore, cannot be easily modified for the collection of additional, research-specific data. With a few notable exceptions, PBRNs are still awaiting the potential of EHRs to revolutionize their data collection capabilities.

**Thick Client (Centralized) Systems**
Data management can be effectively distributed to multiple users at one time with use of networked computers that are running a central application called a thick client. Applications of this nature can guide research assistants through telephone data collection from network members or patients. Error checking for missing and incorrect entries, pick lists (lists from which the user selects a single item or multiple items), and forced data entry (a feature that prevents the user from skipping questions) can be used to improve the reliability of the data collected and speed the collection process. These systems are not efficient options for simultaneous data collection across multiple practices because of the need to either load a copy of the database locally (such as on a notebook computer that is operated off the network) or have a continuous linkage to a central database via a network. A 2001 survey conducted by the Pediatric Practice Research Group (PPRG) found just 40% of responding PBRN members had networked computers in their offices, further narrowing the scope of practices that can incorporate thick client systems.

**Notebook Computers**
Notebook computers offer portability for data entry or collection, combined with the full capabilities of a desktop computer. Examples of the effective use of notebook data collection methods include chart reviews and extractions, and on-site data collection from patient, clinician, or staff interviews. Notebook computers can run a local database, which is easy to program and provides an effective system for studies in which research assistants collect data on-site.

**Internet Browser-Based Systems**
Internet browser-based systems have the advantage of being available from any location with access to the Internet. Most Americans and all medical personnel are familiar with browsing the Internet; thus, most users are comfortable with these systems. Browser-based systems on workstations typically do not require installation of software, and program updates need be made at only 1 location to be immediately available to all users.

**Error Checking With Internet Browser-Based Systems**
Traditional Internet-based systems are excellent for managing complex data sets. Using a desktop computer, users can easily handle either text entries or closed-ended questions. Internet-based systems can offer complex error checking, either centrally or at the browser. The central server can perform error checking, but the data must be submitted first. This process can frustrate users. The longer and more complex a single form becomes, moreover, the more likely it is to contain errors. With central error checking, correcting an error requires reloading the form on the user's workstation, preferably with the errors highlighted. Anyone who has struggled with a complex Internet form, submitting it over and over, knows how frustrating this can be for the user.

A second method of error checking is immediate checking, a method that usually requires advanced programming, typically Sun Java scripting. Java scripting, which is coding that is transmitted with the form to perform actions locally, can speed error checking. The data are checked as the user moves from field to field (much as it is with a traditional thick client system). Unfortunately, Java scripting can make a program less compatible across browsers (eg, Microsoft Internet Explorer, Netscape Navigator, Mozilla) or with older versions of a single browser. This incompatibility is, however, becoming less of a concern as older computers are phased out. Carefully designed screens can improve the reliability of collected data, obviating the need for Java scripting.

**Security for Internet Browser-Based Systems**
If sensitive data will be transmitted through Internet browser-based systems, a PBRN must consider how to
The most effective way to secure data is encryption, which is the translation of data into a secret code. To read an encrypted file, users must have access to a secret key or password that enables them to decrypt it. The easiest way to encrypt sensitive data is to use Secure Sockets Layer (SSL), a protocol for transmitting private documents via the Internet. This protocol uses a private key to encrypt data that are transferred over the SSL connection. By convention, uniform resource locators (URLs) that require an SSL connection start with https instead of with http.\textsuperscript{18}

Additionally, a virtual private network (VPN) can be established that not only encrypts the data, but specifies computer-to-computer access to the data to decrease the chance of interception. Establishing a VPN requires users to load nonapplication-specific software onto their computers and activate it with each use, thus complicating basic Internet use. The increase in security achieved with a VPN comes with a price: a recent study by Ariza et al\textsuperscript{17} found that insufficient staff training and time (among other factors) were obstacles to expanding computer use within PBRNs, indicating that data collection interfaces must be kept simple unless staff can be adequately trained to use new software.

Access to the Internet in PBRN Practices

The Kentucky Ambulatory Network (KAN) recently reported that all but 1 practice responding to an information technology survey had Internet access; however, 43% had only dial-up service (which provides only low-speed transfer of data).\textsuperscript{19} In the PPRG survey, 87% of respondents had Internet access (including e-mail—only access), but just 20% of those had it on all computers, and only 65% of those with Internet access had Web-browsing capabilities.\textsuperscript{16} Limited Internet access, specifically Web access, means that PBRNs must carefully consider which studies should take advantage of Internet browser-based systems. Presumably, these percentages are increasing with time.

Internet-based data collection works best when studies permit data entry after the patient visit as opposed to real-time data collection in the examination room. As an alternative, a paper form can be used for initial collection of data, which are then transferred to an Internet form. This approach shifts the data entry activity to the practice. Although this shift improves data turnaround and may help reduce occurrences of missing data, it adds an additional burden on practices. Internet-based data collection systems seem to be ideal for clinician or staff surveys, particularly if all of a network’s clinicians have access to e-mail. A Wisconsin Research Network (WReN) study found that response rates to Internet-based surveys were higher than those to paper-based ones,\textsuperscript{20} but the Colorado Research Network (CaReNet) found the opposite, as have others.\textsuperscript{21} Schleyer and Forrest\textsuperscript{22} provide a thorough discussion of how to design e-mail surveys to obtain quality results, including a comparison of the costs with those of traditional paper-based surveys.

Personal Digital Assistants

One of the hallmarks of PBRNs is point-of-care data collection. With the heavy penetration of the personal digital assistants (PDA) into clinical care, these devices appear to be the best current option for electronic point-of-care data collection. Ariza and colleagues of PPRG\textsuperscript{17} found 63% of their survey respondents were willing to consider use of handheld touch screen devices.

As PDA systems increase in speed and storage capacity, their ability to provide extensive “just in time” information is impressive. It is logical that PDAs are being heavily explored as a means of capturing electronic data within PBRNs. Point-of-care studies in PBRNs typically have cross-sectional designs that require collection of limited amounts of data. These studies can be done fairly easily with PDA data collection. The experience of CaReNet and other PBRNs indicates that properly designed PDA data collection instruments can often be completed more rapidly than the equivalent paper form. Forced data entry ensures complete data collection, and range checks ensure that the data are logical (although not necessarily correct). Complex algorithms for data collection can be difficult to follow on paper, but branch points and question skipping are relatively easy to program into PDA systems. Thus, skip patterns that appear overwhelming on paper are virtually transparent to PDA users.

Tools for developing software for PDAs lag considerably behind those for more robust computer systems. Further complicating the issue is that few development tools cross the 2 operating systems, Palm OS (PalmSource, Sunnyvale, Calif) and Windows Pocket PC (Microsoft, Redmond, Wash), well. If a PBRN relies on members to supply their own PDAs, data collection instruments will likely need to be developed for both systems. Additionally, clinicians who use their PDA extensively to facilitate patient care may have little memory available on the device for additional programs. Newer development software may not operate on older versions of PDA operating systems. Newly introduced tools, such as Microsoft .NET, offer hope for powerful, cross-platform development tools.

The small screen size of PDAs along with tedious text entry also must be taken into consideration when developing data collection systems.\textsuperscript{23} Text fields are difficult to implement as character recognition or
on-screen keyboards are relatively slow and prone to errors. Pick lists and numbers work well. Nonetheless, care should be given to the number of selections available. Most PDA screens support approximately 12 lines of viewable text. Single-item pick lists (often displayed as a drop-down list) are easy to program, but if the list is long, searching for the correct answer is not as easy with a PDA as it is with more robust computers. If the question involves selection of multiple items and more than 8 to 10 items are offered, then some will not be displayed on the screen and will require scrolling to be selected. It is difficult to guarantee that users will scroll down and view items that are off the screen, especially in light of the time constraints of point-of-care data collection. When the list includes easily recognized data elements, such as months, users quickly understand that additional information must be available off the screen. But long lists of items that are project specific, such as a list of services provided during a visit, will not immediately prompt the user to scroll for hidden items. Lastly, the small screen size typically means that questions are displayed one at a time in a sequential fashion. This sequence works well when the data collection can be logically ordered, but can be frustrating when data entry is less predictable, such as when recording selected items from a patient history. Thus, developers need to be cognizant of the strengths and limitations of PDAs, and use them only for studies in which these computers enhance data collection.

Synchronizing PDAs across a large network can be challenging. Firewall administrators may block ports necessary to synchronize data between the central server and the user’s PDA. Newer development systems that are moving to XML (extensible markup language) for data transfer may help eliminate some of these problems. Before a PBRN invests in PDA development and synchronization software, however, a critical first step is testing synchronization with network administrators across a network.

Tablet PCs
The final option we describe for electronically collecting research data is tablet PCs, tablet-sized computers. Tablet PCs are thin, lightweight computers that allow users to enter data on a touch screen. Several models are available; most weigh less than 2 lb and are about the size of a 500-page spiral notebook (9 in × 11 in × 1 in). Tablet PCs have reasonably sized hard drives (typically 6 to 20 GB) and run full operating systems, typically Microsoft’s Windows XP Tablet PC. Tablet PCs cost between $800 and $3,500, depending on the operating system and features.

Tablet PCs offer portability and the ease of using a touch screen system for navigation. With an extended array of development tools and the capability of storing a large volume of data, tablet PCs overcome many of the limitations of typical PDAs. Because of the higher price and larger size of tablet PCs, physicians are unlikely to carry them for intermittent point-of-care data collection, such as during a typical card study, unless they are in use in the practice. Tablet PCs are well suited for delivering multimedia messages to patients or facilitating data collection directly from patients. Interactive models that allow the patient to use the device and then deliver it to the clinician for further data collection are also possible.

PBRN EXPERIENCE WITH ELECTRONIC DATA COLLECTION: SOME EXAMPLES
As the previous section indicates, a number of technologies have the potential to facilitate electronic data collection in PBRNs. Table 2 highlights issues in matching these technologies to the study design. In this section, we provide examples of various PBRNs’ experiences with electronic data collection.

Data Mining
Data mining has been a part of PBRN research for decades. ASPN used data mining primarily to create age-sex and morbidity profiles of member practices. Even these data elements, contained within billing

<table>
<thead>
<tr>
<th>Technology</th>
<th>Network Distribution Capability*</th>
<th>Connectivity Across Multiple Systems</th>
<th>Continuity or Longitudinal Data</th>
<th>Ease of Development</th>
</tr>
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<tbody>
<tr>
<td>Mining existing data sources</td>
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<td>+</td>
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<td>Tablet PCs</td>
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<td>Thick client</td>
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<td>Internet-based system</td>
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<td>PDA</td>
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<tr>
<td>Notebook computer</td>
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</tbody>
</table>

Symbols indicate if, for addressing a given issue, the technology is strongly recommended (+ +), is recommended (+), is neutral/varies no recommendation (+/−), may work (−), or is not recommended (− −).
PDA = personal digital assistant.
* Based on mining data from more than 1 system. Data mining might be more feasible is only a single system is used.
data sets, were difficult for some practices to supply electronically. Outside the PBRN arena, efforts of Irish general practitioners to collect morbidity data from computerized systems met with major difficulties due in part to problems with extracting data from practice software systems and the need for a high level of dedicated staff and resources to implement such a project. Today, virtually all practices have these data in electronic form, although retrieving them in a uniform manner across a large PBRN can still be a difficult undertaking.

Data mining using clinical data within an EHR is finally becoming a reality. Successful ventures to date have all come from PBRNs that use a single EHR system. The Practice Partner Research Network (PPRNet) has created a longitudinal patient database composed of data from the Practice Partner Patient Record from participating physicians throughout the United States. The network has focused on translational activities through data synthesis and on providing practices and clinicians with feedback to improve care.

Perhaps the most advanced data system within the United States that supports a PBRN is the Regenstrief Medical Record System used by Indiana University Medical Group–Primary Care (IUMG–PC), a single-practice organization that contains IUMG–ResNet, an urban primary care PBRN. This system has been in operation since 1972 and contains hundreds of millions of discrete coded observations, although many of these data originate from specialist or hospital care. The Regenstrief Medical Record System has been a rich source of clinical data, resulting in hundreds of articles in the past 4 years alone. It can be programmed to provide study reminders and has powerful tools for supporting subject recruitment in PBRN offices. The system can extract existing clinical data and link it to data collected at the point of care, thus lessening the burden on the clinician and the practice. With access to data extending back for many years, powerful epidemiologic studies from primary care practices are emerging.

Henk Lamberts and Inge Hofmans-Ookkes created an episode-oriented EHR system, called Transhis, that is used by a network of general practitioners in the Netherlands. In this system, the application of the International Classification for Primary Care (ICPC) is the guiding principle to structure episode-oriented epidemiology. Transhis contains more than 300,000 patient-years of data. The system has been modified to collect specific research data based on selected diagnoses for time-limited studies. The Transition Project is aimed at the further development of episode-oriented epidemiology in general practice, both in the Netherlands and elsewhere. The system used in this project highlights a data model that supports primary care research with point-of-care physician coding.

PBRNs in which all members share the same EHR have successfully used their clinical data systems for research. The challenge facing most PBRNs is to develop approaches that will allow them to aggregate data across disparate EHR systems. Efforts to standardize national data should facilitate data sharing across systems, but a PBRN's activities entail more than data mining, and mixing clinical and research data collection within an EHR system is still rare.

Web Forms and Databases

For many years, the Dartmouth COOP has incrementally developed and tested a patient-centered, Web-based information system specifically designed to support a more productive interaction between the patient or caregiver and the practice team (see http://www.howsyourhealth.org). How’s Your Health (HYH) is a free, Web-based survey providing patients with tested, evidence-based health information and an action form designed to help patients take better care of themselves and work more closely with their physicians.

HYH was developed to link consumers with tools that allow them to become more actively involved in preventing and managing their health care problems, and to provide physician offices with resources to help them operate more efficiently and encourage consumers to participate in their own health care. In this project, patients enter information through a Web interface or through a handheld device in a clinician’s office. Using these data, the system then provides patient-specific education and recommendations for the patient and clinician, as well as aggregated data for research. The system blends various data entry options and user views into a single database. This novel population-based research approach bridges community health and practice-based research.

Several PBRNs operate clinical databases that are also used for research. These systems use a paper interface with the clinician- and practice-level data entry. We will not discuss them further here.

Web-based collection of information related to medical errors has been successfully implemented in a number of networks, including CaReNet, the American Academy of Family Physicians National Research Network, and many nonresearch institution-based systems. Clinicians and staff appear able to remember the details of an error sufficiently well to delay their report until they have time and access to the Internet. An early comparison of Web with paper reports indicated that clinicians were comfortable providing error information over the Internet, and the reports appeared more detailed when they were submitted electronically than when they were handwritten.
Tablet PCs for Data Collection
CaReNet successfully programmed tablet PCs to administer separate sections of a national survey—the Primary Care Network Survey (PRINS)—to the front office staff, the patient, and the clinician. This approach to data collection allows linked data collection from the patient, clinician, or office staff member, while maintaining an anonymous format, if desired. Patients helped steer the data collection process to clinicians and staff after completing their portion of the survey.

An instructional demonstration guided users through the use of the tablet PC. After patients completed the PRINS survey, exit interviews were conducted to evaluate their experience with the tablet PC. Patients had favorable reactions to the technology. Overall, patients were able and willing to use tablet PCs for data collection within busy primary care offices. Increasing patient involvement in practice-based research may be possible through the use of this technology, which allows patient-directed data collection at a single point in time or longitudinally. Since the PRINS study concluded, the capabilities of reasonably priced tablet PCs have improved, expanding their ability to support data collection from patients and staff.

Multicomponent Data Collection
The Oklahoma Physicians Resource/Research Network (OKPRN) and a number of collaborators developed the Influenza-Like Illness Surveillance and Messaging System (ILI-SMS), a surveillance system for the reporting of influenzalike illness and other acute syndromes. The ILI-SMS regularly sends public health messages to clinicians, and the clinicians, in return, send daily reports to the Oklahoma State Department of Health on cases of influenza-like illness during influenza season. This system is designed for operation by nurses, although front office staff or clinicians can also use it.

Four interfaces have been or will be developed for the ILI-SMS: (1) a Web interface for data entry and retrieval using an Internet-connected computer, (2) a hard-wired PDA interface that transmits and retrieves data through the PDAs “hot sync” function, (3) a Bluetooth PDA interface that transmits and retrieves data wirelessly through the clinic’s wireless local area network, and (4) a wireless PDA interface for PDA and mobile phone devices that transmits and retrieves information over a cellular network. Prompts, flow sheets, and audits can be printed directly from the computer or from the PDA via an infrared printer port, or through the wireless local area network in the case of Bluetooth-enabled PDAs.

The ILI-SMS has been tested in 29 OKPRN practices. Of these, 27 reported surveillance data on a daily basis more than 90% of the time during a 2-month period. The 549 reports captured 10,892 patient encounters, including 529 cases of influenza-like illness and 29 hospitalizations of patients with such illness.

Clinicians expressed great satisfaction with the feedback they received from the Oklahoma State Department of Health, as they were able to follow the spread of influenza across the state, anticipating the need for additional appointment slots. They indicated that the burden of reporting influenza-like illness was minimal compared with the benefit of the information derived from it. These results suggest that offering multiple options for data collection, feedback, or both within a single project improves acceptability across users and locations.

SHOULD A PBRN PURSUE ELECTRONIC DATA COLLECTION?
Obviously, not every PBRN is ready to pursue electronic data collection. Young PBRNs that are still recruiting initial members, that are focusing on their first studies, or that have limited personnel may wish to direct their resources and energy toward other infrastructure. When considering electronic data collection, PBRN directors should ask themselves the following questions:

• Do the studies we wish to pursue lend themselves to electronic data collection?
• Do we have the technologic expertise to implement electronic data collection?
• Can we support the infrastructure and personnel costs associated with electronic data collection?

Table 3 lists some of the specific issues that PBRN directors should consider before developing electronic data collection methods.

CONCLUSION
In this article, we have discussed a number of options for collecting data from PBRN members. PBRNs should not assume that any one electronic data collection method will meet all their needs. Administrative costs, the burden on practices and clinicians, and issues of training and data quality moreover must all be weighed in a decision about whether to collect data electronically. PBRNs are rapidly expanding and experimenting with options for electronically collecting and communicating data. While some networks have successfully developed a primary approach for electronic data collection, all will need to match their data collection options with their project requirements. Some networks have begun sharing resources and knowledge to help
advancing the use of technology and PBRN methods. As PBRNs expand their efforts at translational research, the line between quality improvement and research will continue to blur, as will the distinction between clinically oriented and research-oriented data systems.

PBRNs are well positioned to serve as the primary laboratories to study and improve the delivery of primary care. A critical ingredient in this effort is the improved capacity to collect high-quality data using electronic methods. These methods help networks conduct research effectively and efficiently, and make it possible to collect data longitudinally as well as to conduct studies that are national in scope. Supporting a wide variety of data collection formats is difficult for any single PBRN, and collaborative efforts hold great promise for this effort. Recent support by the Agency for Healthcare Research and Quality initiatives to promote connectivity of health data across a state should help PBRN research activities through enhanced data connectivity. Two National Institutes of Health pilot projects to support multi-PBRN research projects, including electronic data collection, are likely to further speed innovation. We hope that these efforts will lead to greater collaboration and the development of a national infrastructure to support primary care PBRN research.

To read or post commentaries in response to this article, see it online at http://www.annfammed.org/cgi/content/full/3/Suppl_1/S21.

Key words: Practice-based research network; computer communication networks; data collection; computers, handheld; database management systems; research design; Health Insurance Portability and Accountability Act; informed consent; health services research

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**Table 3. Selected Technical Issues to Consider When Developing an Electronic Data Collection System**

<table>
<thead>
<tr>
<th>Issue</th>
<th>Technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>What hardware will you be using?</td>
<td>Workstation or desktop computer in office&lt;br&gt;PDA supplied by the network&lt;br&gt;PDA supplied by the clinician&lt;br&gt;Pen-tablet computer&lt;br&gt;Slate&lt;br&gt;Convertible Web server for hosting data forms&lt;br&gt;Does it have a security certificate to run SSL?&lt;br&gt;Web server for synchronization (does not have to be a separate server)&lt;br&gt;Does it have a security certificate to run SSL?&lt;br&gt;Database server&lt;br&gt;Application server (could be the database server or the Web server in a minimal configuration)</td>
</tr>
<tr>
<td>What software will you be using?</td>
<td>Operating system for the Web server(s)&lt;br&gt;Windows&lt;br&gt;Linux&lt;br&gt;Unix&lt;br&gt;Web services software (IIS, Apache, others)&lt;br&gt;Security&lt;br&gt;SSL with certificates&lt;br&gt;VPN&lt;br&gt;Development software&lt;br&gt;ASP&lt;br&gt;.NET&lt;br&gt;Visual Basic/C++&lt;br&gt;Power Builder&lt;br&gt;ColdFusion and others&lt;br&gt;One of many PDA development systems&lt;br&gt;One of many Web survey tools&lt;br&gt;Third-party controls for specific activities&lt;br&gt;One of several database systems</td>
</tr>
<tr>
<td>Network and workstation issues</td>
<td>Who has administrative rights to office workstations?&lt;br&gt;Who administers the fire wall for the PBRN and/or its service provider?&lt;br&gt;Who administers the fire wall for each practice in the network?&lt;br&gt;What types of networks and connectivity are in each practice?&lt;br&gt;Broadband&lt;br&gt;Dial-up modem&lt;br&gt;Wireless within office&lt;br&gt;LAN&lt;br&gt;WAN</td>
</tr>
<tr>
<td>Personnel issues</td>
<td>Who will develop the data collection forms?&lt;br&gt;Who will manage the database, including security and fail-safe mechanisms?&lt;br&gt;Who will train practice staff and clinicians to use the system?&lt;br&gt;What level of support for the system is required?&lt;br&gt;24 hours per day, 7 days per week&lt;br&gt;8:00 AM-5:00 PM Monday through Friday&lt;br&gt;Less-intense support</td>
</tr>
<tr>
<td>Replacement issues</td>
<td>Who will pay to replace equipment as it ages?&lt;br&gt;Central hardware and software&lt;br&gt;Practice-level hardware</td>
</tr>
</tbody>
</table>

PDA = personal digital assistant; SSL = Secure Sockets Layer; VPN = virtual private network; ASP = Active Server pages; PBRN = practice-based research network; LAN = local area network; WAN = wide-area network.
References


Human Subjects Issues and IRB Review in Practice-Based Research

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ABSTRACT

PURPOSE This article explores the challenges that practice-based research networks (PBRNs) face with respect to the regulatory requirements for institutional review board (IRB) review and the protection of human subjects in research.

METHODS We used a regulatory and literature review, our previous research involving PBRN researchers, and our experience to identify issues in regulatory compliance and human subjects protections that present challenges to PBRNs and to suggest possible responses.

RESULTS We identified 3 challenges that PBRNs face with respect to regulatory compliance and human subjects protections. First, ensuring compliance with federal regulations governing human subjects research across all participating practices may be difficult. Clinicians may be unfamiliar with the regulatory requirements and may not have access to an IRB that can provide the required protocol review; moreover, different IRBs may impose inconsistent requirements. Second, conducting research in the practice setting presents unique issues regarding identification of human subjects, consent, and confidentiality. Finally, the use of electronic databases across practices for research raises concerns about how to respect the wishes of participants when combining data and how to maintain confidentiality of data.

CONCLUSIONS PBRN research makes unique contributions to the clinical evidence base by collecting data in community settings where most clinical care is provided. Such research, however, also presents unique challenges to human subject protections and regulatory compliance. Addressing these challenges is necessary to maintain public trust in and support for PBRN research. With careful planning, these ethical and regulatory challenges can be overcome.


INTRODUCTION

Concerns that clinical research conducted in tertiary care centers was not generalizable to the primary care setting led to the development of practice-based research networks (PBRNs). Practice-based research focuses on questions relevant to community-based patient populations in the primary care setting. Unlike single-site research, practice-based research conducted in PBRNs takes place across many sites in busy practices in the community. As a result, the research can provide a more accurate picture of illness and health care in the community. The participating practices, however, may not have the same resources as a network of academic research centers. Although many drug companies reimburse the costs of clinical research in physician offices, PBRNs generally do not.

PBRN research raises special challenges regarding regulatory compliance and human subjects protections. In this article, we focus on 3 of these challenges. First, ensuring compliance with federal regulations governing human subjects research across all participating practices may be difficult. Clinicians may be unfamiliar with the regulatory requirements and may...
not have access to an institutional review board (IRB) that can provide the required protocol review. We suggest ways for ensuring compliance and facilitating review. Second, conducting research in the practice setting presents unique issues regarding identification of human subjects, consent, and confidentiality. Patients may not understand how they are involved in the ongoing research, and practices and staff may be involved as subjects, researchers, or both. In addition, the practice setting may pose different risks to confidentiality. We suggest ways for thinking through these issues and respecting the interests of the patients, practice, and staff. Finally, the use of electronic databases across practices for research raises special concerns. We provide specific suggestions for addressing these issues.

REGULATORY ISSUES:
IRB REVIEW AND ASSURANCES

Obtaining necessary IRB review may be challenging for PBRNs working in multiple practices.\textsuperscript{5,6} We have identified 3 primary challenges. First, practices may not be aware of the need for IRB review. Practice-based physicians may not have research training and may not be aware of the regulatory requirements. PBRNs may need to help participating practices understand those requirements and ensure compliance. Second, many practices may not have access to an IRB because they are not affiliated with an academic medical center or hospital. Finally, the need to obtain approval from multiple IRBs may lead to inconsistent requirements at different sites, and PBRNs need to know how to respond to these differences.

Required IRB Review and Assurance of Compliance

Research involving human participants raises ethical concerns because individuals may experience risks and inconveniences primarily to benefit others by advancing scientific knowledge. Federal regulations govern research involving human participants. The Federal Policy for the Protection of Human Subjects—also known as the Common Rule, codified by the Department of Health and Human Services (HHS) regulations at 45 CFR part 46, Subpart A—applies to human subjects research conducted or supported by any of the 16 federal departments and agencies that has adopted the Common Rule.\textsuperscript{7} In addition, institutions with an HHS-approved Federalwide Assurance (FWA) often apply those regulations to all human subjects research conducted at their institution. Although the Common Rule is most relevant to PBRN research, there are also separate Food and Drug Administration regulations that apply to research regulated by this agency.\textsuperscript{8}

Institutions engaged in human subjects research conducted or supported by HHS are required to provide written assurance of compliance with the regulations, including designating the IRB or IRBs that review the research. The most common assurance being submitted is the FWA. The secretary of HHS has delegated authority to approve these assurances to the Office for Human Research Protections (OHRP). OHRP provides guidance to help determine when an institution is engaged in human subjects research.\textsuperscript{7}

Institutions engaged in human subjects research that is subject to the HHS regulations must have an OHRP-approved assurance of compliance and certify that the research has been approved by an IRB before any research commences.\textsuperscript{9} These requirements apply to all research, not otherwise exempt, involving human participants, including pilot studies. HHS regulations define research as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.” A human subject is defined as “a living individual about whom an investigator … conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.”\textsuperscript{9} The type of IRB review that is required will depend on the level of risk presented by the study.\textsuperscript{9} The primary focus of the IRB review is on the safety and well-being of research participants.\textsuperscript{10}

Practice-based physicians may not be aware of the federal regulations governing research. Most physicians will not have received training in clinical research or human subjects protections. Some practice-based research moreover may resemble quality improvement efforts that physician practices routinely undertake without IRB oversight. For example, a PBRN may undertake a study to increase use of cholesterol-lowering drugs in patients for whom they are recommended.\textsuperscript{11} Although physicians could undertake this effort to improve quality of care within their practice, which would not be considered research, when the PBRN does so, it undertakes a systematic investigation to develop or contribute to generalizable knowledge and that would be research. If the data are obtained through an intervention or interaction with a living individual or are identifiable private information about a living individual, the project falls within the federal definition of human subjects research.

PBRNs, therefore, should be prepared to help practices understand and comply with these regulations. The requirements of the regulations should be explained early to practices interested in participating in the network or a given project. For example, in the Digitalis Investigation Group (DIG) trial, a large clinical trial conducted by the National Heart, Lung,
Facilitating Review of PBRN Research

PBRNs can help participating practices obtain the necessary IRB review. This assistance may entail helping them obtain a federal assurance, identifying an appropriate IRB, and helping them prepare their IRB applications. One multisite trial group found that three fifths of the time required for protocol approval was devoted to preparing the IRB submission and making required revisions. Coordinating IRB submissions through a network committee might reduce the time required for approval, reduce the burden on individual investigators, and enhance consistency across sites.

A PBRN may want to explore options to minimize the number of IRBs required for its research. These options are particularly appropriate because PBRN research takes place at multiple sites; involves a stable, well-defined group; and often presents only minimal risk to participants.

Centralized IRB Review

In centralized IRB review, 1 IRB takes primary responsibility for review on an ongoing basis. The National Cancer Institute Central IRB (CIRB) pilot project and the Multicenter Academic Clinical Research Organization (MACRO) are examples of centralized IRB review. In both groups, a central IRB conducts the primary review, with administrative review by local IRBs to determine whether to accept the approval of the central IRB and conduct the research at their institution (Table 1). Some groups with their own national IRB, such as the American Academy of Pediatrics, have used the national IRB to provide a centralized IRB in some cases. Investigators at institutions with their own IRB may still need to undergo review at their own institution, however, unless the institution designates the national IRB as their IRB of record for the protocol.

Centralized review has problems that need to be worked out. Institutions may be reluctant to rely on another IRB. Current centralized review models generally do not eliminate local IRB review, although the authority of the local IRB to request changes may be

<table>
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<tr>
<th>Model</th>
<th>Example</th>
<th>Central Review</th>
<th>Local Review</th>
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<tr>
<td>Newly established national IRB</td>
<td>CIRB: A national IRB of the NCI composed of people with cancer expertise across the country who are not NCI employees</td>
<td>The CIRB conducts initial review of all NCI phase III cancer-related trials</td>
<td>Local IRB review occurs after CIRB review. Local IRBs may approve without changes, a &quot;facilitated review,&quot; or conduct their own review. Local IRBs, however, may not change the approved protocol— they can only disapprove participation of researchers from their institution</td>
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<tr>
<td>Designated primary IRB among a</td>
<td>MACRO: A consortium of 5 universities that collaborate on multisite trials</td>
<td>A participating university IRB serves as the IRB of record for a given protocol (the assignment rotates among the 5)</td>
<td>The IRBs of the 4 other universities conduct only administrative review (review with less than a full IRB committee) of the approved protocol to ensure that local issues have been addressed</td>
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IRB = institutional review board; CIRB = Central Institutional Review Board; NCI = National Cancer Institute; MACRO = Multicenter Academic Clinical Research Organization.
limited. Establishing a centralized IRB takes considerable time and effort. PBRNs need to judge whether there is sufficient benefit to justify those efforts.

**Relying on Other IRBs**

PBRNs may be able to minimize multiple IRB reviews by getting institutions involved in the network to agree to rely on an external IRB’s review. This arrangement may be achieved through a formal agreement. The Beta-Carotene and Retinol Efficacy Trial (CARET), a multisite chemoprevention trial, provides an example of this approach. The CARET group obtained an agreement from all the CARET institutions designating, for that single study, that the IRB at the coordinating center would serve as the IRB of record for all research involving its repository, although local IRBs could modify or restrict the central IRB’s decision. In this particular case, institutions may have been more willing to agree to a central IRB because the trial’s intervention had ended and the data and the trial activities were centralized.

When a PBRN relies on an external IRB for review of a protocol, the PBRN and the reviewing IRB should develop a formal agreement. The agreement may cover 1 protocol, several protocols, or a program of research. The signatory official of each institution should sign the agreement. The initial review and continuing oversight of the reviewing IRB must comply with the terms of the PBRN’s OHRP-approved assurance. The PBRN should take responsibility for ensuring compliance at all sites with the IRB’s determinations and with the terms of their assurance. OHRP provides a sample IRB Authorization Agreement that outlines the scope of the responsibilities for the IRB and the PBRN.

PBRNs may develop other mechanisms for streamlining IRB review. For example, one PBRN has requested that the chairs of the 3 IRBs with whom it works most frequently use conference calls to address jointly low-risk, practice-based research protocols that qualify for review under the expedited process. Although face-to-face meetings are strongly recommended, OHRP recognizes that circumstances at times warrant IRB meetings to be conducted by telephone conference call, provided “each participating IRB member: (i) has received all pertinent material prior to the meeting, and (ii) can actively and equally participate in the discussion of all protocols.”

In some instances, it may be beneficial to form a new IRB to take responsibility for a portion of or the whole PBRN. For example, a group of unaffiliated investigators who are also involved in research beyond the PBRN might establish their own IRB to review all research in which the group is involved. It may be difficult, however, to identify members who could provide independent oversight. Alternatively, PBRN investigators who are unaffiliated with an IRB may establish an IRB to provide overall review for the PBRN. If a group decides to form an IRB, they should consult the regulations and the OHRP Web site, which contains complete instructions and forms for registering an IRB. The PBRN may want to assist the investigators with this process. In the DIG trial, for example, the coordinating center helped 354 centers establish their own IRB or find another one willing to take responsibility for the center.

Establishing a PBRN IRB could help avoid problems commonly encountered in obtaining IRB review for PBRN research. It could minimize the number of multiple reviews and, therefore, potentially conflicting recommendations. It is unlikely, however, to eliminate multiple reviews entirely, particularly if some PBRN investigators have affiliations with academic medical centers. In addition, it may be costly in terms of time and money to set up and maintain the IRB. PBRNs will need to consider their own experience with obtaining IRB review to determine whether establishing a separate IRB would be beneficial.

**Role of Accreditation in PBRNs**

The accreditation of an institution’s human subjects protection program may facilitate PBRN efforts to centralize review functions. For example, if accreditation becomes accepted as a mark of excellence, other institutions may be more willing to rely on an IRB that has received accreditation.

**Individual Investigator Agreements**

An institution with an OHRP-approved FWA may extend their assurance to cover an external investigator who is collaborating and engaged in human subjects research at another institution that does not routinely conduct such research. The current mechanism used to do this is the Individual Investigator Agreement, which is available on the OHRP Web site. Some PBRNs have been successful in getting an internal IRB at the host FWA institution to take responsibility for unaffiliated investigators covered by this agreement.

**Addressing Differing IRB Requirements**

IRBs reviewing the same protocol may impose different requirements. For example, in one multisite clinical trial of a treatment for asthma, IRB responses ranged from believing all patients should receive the experimental intervention to believing that the intervention was so dangerous that no patient should receive it. In that study, which involved 44 sites, 80% of IRBs asked investigators to make revisions to the standard protocol.
Meeting different IRB requirements not only can be frustrating, but also can affect the study outcome. In a multisite health services research study, IRB requirements for contacting potential research subjects at different sites were associated with participation rates. Some IRBs permitted release of contact information to investigators without specific advance permission from potential participants, whereas others required oral advance permission and some required written advance permission to release the contact information. The response rate varied widely by contact mode, presenting a threat to study validity.33

When faced with different IRB requirements, PBRN investigators need to consider whether to make the protocol conform across all sites and, if not, whether to inform other IRBs reviewing the protocol of the changes required by 1 IRB. To answer these questions, PBRN investigators need to consider what the changes are. Many IRB requirements may affect only the documentation of the study, not its substance. For example, an IRB may request changes to the consent language to reflect locally approved language. When the underlying meaning is the same, an investigator may reasonably accept differences between sites without informing other IRBs about the requested changes.

A different approach is required when some IRBs require substantive changes to the study procedures or the selection of subjects. In such cases, the investigator should either inform all IRBs or drop nonconforming sites from the study. Some changes may undermine the study validity. For example, study participants at sites where the IRB requires written advance permission to contact individuals about study participation may differ considerably from those at sites where such permission is not required. Investigators can try to work with the IRBs to reach agreement. If the threat to generalizability is deemed unacceptable, however, investigators may need to drop the sites where written advance permission is required. Investigators cannot ethically involve human subjects in research if the research is not likely to yield valid answers to the research question.5,34 Investigators should also inform other IRBs if 1 IRB raises a serious ethical concern about a study. Although not required by the regulations, doing so will help ensure the issues have been adequately considered by these IRBs and preserve the investigators’ relationship with the IRBs that review PBRN research.5

**HUMAN SUBJECTS ISSUES IN PBRN RESEARCH**

PBRN research also presents unique issues related to protection of human participants. Network clinicians may participate both as researchers and as research participants, and may involve their staff and patients in research. As a result, determining who the subjects of the research are and, therefore, who needs to consent may be challenging. In addition, practice-based research may require special attention to protecting confidentiality and minimizing risks within the practice setting.

**Who Are the Subjects?**

As discussed earlier, the HHS regulations define a human subject as “a living individual about whom an investigator … conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.”8

Increasingly, PBRN research involves interventions to change practices and clinician behaviors. Projects may address patient issues, practice issues, or both. Accordingly, determining who the research subject is in PBRN research may be more complicated than doing so in traditional biomedical research. For example, in a study designed to look at physician prescribing practices, the physicians who are asked to fill out a questionnaire may be the only subjects. If the study is designed to conduct chart reviews to validate questionnaire responses, however, both physicians and patients may be considered subjects. Similarly, a study of the effects of a computerized disease management system might focus on the clinician, the practice staff, or both. However, if patient satisfaction is an important outcome, then patients also might be subjects. PBRNs need to think carefully about how clinicians, staff, and patients are involved in each study to determine which groups meet the human subjects definition.

**Who Must Consent?**

All subjects must voluntarily consent to their participation in research, unless the requirement is waived under the regulations.35 In many cases, PBRNs may rely on medical directors or practice leaders for access to the practice. Their permission may be necessary to approach physicians, staff, or patients, and to implement interventions within the practice. This permission, however, may not meet ethical and legal consent requirements for study participation. In some studies, clinicians and staff may fall within the federal definition of human subjects from whom informed consent is legally and ethically required. For example, a study of the effectiveness of computer reminders in increasing adherence to practice guidelines (eg, ordering of recommended tests) might randomize practices to the intervention or a control condition. Because the investigators obtain data about the clinicians and their staff through an intervention involving them, however, their consent would be required. In other studies, consent
IRB REVIEW IN PRACTICE-BASED RESEARCH

may not be required under the regulations. For example, if a study is designed to review medical records to determine how often recommended tests are ordered, without obtaining identifiable information about the physicians, consent may not be required. It would be ethically preferable, however, to inform clinicians and staff about the research, give them an opportunity to ask questions, and, in some cases, allow them to opt out. As a practical matter, informing clinicians and staff about research taking place in the practice may improve implementation of the research project.

When Is Consent Not Required?
Under the HHS regulations, there are 2 circumstances in which informed consent is not required: when the research is exempt from the regulations and when consent may be waived.

Exempt Research
Research involving surveys, interviews, or observation of public behavior, and research using existing records may be exempt from the federal regulations provided that data are recorded in such a way that the human participants cannot be identified either directly or through linked identifiers. Research involving surveys, interviews, or observations of public behavior is not exempt if disclosure of responses “could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects’ financial standing, employability, or reputation.” Retrospective chart reviews, accordingly, may be conducted without specific patient consent, provided that identifying information about the patients is not recorded, directly or through identifiers linked to the patients. Individual IRBs, however, may be stricter than the regulations and may require IRB review and consent. In addition, IRBs may no longer consider collection of some data (such as dates) as exempt if it includes any of the 18 identifiers specified in the federal privacy regulations mandated by the Health Insurance Portability and Accountability Act (HIPAA). In this supplement, Pace et al provide a detailed discussion of the HIPAA regulations and PBRN research. Research that poses minimal risk but does not qualify as exempt may be eligible for review under the expedited process.

Exemption from the regulations does not necessarily mean that there is no IRB oversight. Many IRBs do not allow investigators to determine exempt status themselves, but rather have a formal process for reviewing such determinations. This process tends to be quick and simple. Because journals increasingly are requiring evidence of IRB approval, it would be prudent to consult with IRBs about exempt status, even if they do not require formal review.

Waiver of Consent
Research that is not exempt may be eligible for waiver of consent under the HHS regulations when the IRB finds and documents all of the following:

- The research involves no more than minimal risk,
- The waiver will not adversely affect the rights and welfare of participants,
- The research could not practicably be carried out without the waiver, and
- The subjects will be provided with additional pertinent information after participation.

Often IRBs may waive consent for medical record reviews that are not exempt (eg, those that do not yet exist at the time the research is proposed); however, it is for the IRB to decide whether all 4 requirements to waive consent have been met, and IRBs may differ in their application of the waiver requirements. If the study involves protected health information, a waiver of HIPAA authorization is also required. Some research topics, such as research on substance use, mental health, and reproductive issues, may present more than minimal risk and therefore may not qualify for waiver of consent.

Even when consent is not legally required, it may be ethically desirable to get patients’ permission to use their information in research. Patients may not be aware that their information may be used in research, and some may object to such use. Notifying patients that their medical records may be used in research alleviates some of this problem. For example, one PBRN has physicians display a certificate to inform patients about research that is taking place in the practice. However, it may be more respectful of patients’ interests to obtain explicit consent to share their information within the PBRN. For example, practices might ask patients to consent to all records research conducted within the PBRN when they enter the practice and annually thereafter. If practices choose simply to notify patients of research within the practice, they should perhaps consider having a procedure for patients to opt out.

Voluntary Consent
PBRNs also should consider how to ensure that consent is voluntary. The personal and professional relationships within the practice may influence the consent process. For example, staff may feel that they cannot refuse their employers’ request to participate in a research project. Similarly, patients may be reluctant to refuse their physicians’ request to participate in research. In questionnaire studies, wherein the risk is minimal and the respondent could turn in a blank questionnaire, this concern may not be an important one; however, in other types of studies, PBRNs should consider steps to protect voluntary choice. In recruiting staff for focus groups, for example, PBRNs could use indirect recruit-
Confidentiality in PBRN Research

PBRNs should also consider how the research setting may affect risks to confidentiality. For example, office staff conducting chart reviews may be more likely to know patients personally. In addition, some research about the practice could present risks to staff. For example, a study of medical records or an interview study could reveal a failure to follow practice guidelines. The risk may be greatest when staff members' supervising physicians are participating as researchers and have access to the study data. Patient or practice characteristics may make it difficult to protect respondent identities in this context. PBRNs need to develop strategies for protecting participants' confidentiality in these settings. In some cases, it may be enough to keep raw data from participating physicians and researchers, and code the research sites so that they cannot be identified. In other cases, it may be appropriate to restrict practices from participating if their physician is participating as a researcher.

RESEARCH DATABASES AND PBRN RESEARCH

The full potential of a PBRN may be realized by combining information across practices within the network. But combining research and medical data across time and across the network raises ethical issues.

The primary ethical issues raised by PBRN research databases are how to respect the wishes of participants when combining data and how to maintain confidentiality of data. For example, some participants may have placed limits on the use of their data by researchers outside the practice or outside the network. Procedures need to be in place to ensure that data are used only in ways authorized by the participants. In addition, the PBRN must take steps to maintain the confidentiality of the data. This measure typically requires sophisticated programming support, which may not be available within the network. Programming support is especially necessary to preserve confidentiality of patient information within a central database that will be updated with new clinical information. Even if it is possible to de-identify data when providing them to researchers, some identifiers will need to be retained to permit the updating. In addition, for some research questions, it may not be possible to work with de-identified data. To protect against unauthorized access, the PBRN may want to isolate the computer from the Internet except when transferring data. If the computer is connected to the Internet, it should be protected by a fire wall and its antivirus software must be updated regularly. If data are transferred through the Internet, this transfer should only be through a secured connection and data should be encrypted. All data should be protected with strict passwords—ones that are not obvious, are not shared, and are changed regularly. To further protect confidentiality of the database, PBRNs should consider obtaining a federal Certificate of Confidentiality to protect against compelled disclosure of identifiable information through a subpoena. PBRNs may additionally wish to ask researchers and their staff with access to the database to affirm that they will maintain its confidentiality and not seek to reidentify individuals whose records are contained within it. As Pace et al describe in their accompanying article, PBRNs need to carefully consider what information will be shared with whom to determine what their obligations are under the privacy regulations. In addition to reading that article, PBRN researchers may want to consult the HHS guidance on the HIPAA Privacy Rule for the research community, which is available online (http://privacyrule-andresearch.nih.gov). Because the privacy regulations are complicated and new, IRBs at different institutions may apply these regulations differently.

CONCLUSIONS

PBRN research makes unique contributions to the clinical evidence base by collecting data in community settings where most clinical care is provided. PBRN research thus provides information on the effectiveness of interventions in actual practice. The NIH Roadmap embraces this concept of clinical research and calls for the expansion of community-based research and research networks. Such research, however, also presents unique challenges to regulatory compliance and human subject protections. Addressing these challenges is necessary to maintain public trust in and support for PBRN research and to collect information on the outcomes in actual clinical practice. In addition, failure to do so may jeopardize publication of research results. With careful planning, these ethical and regulatory challenges can be overcome.

To read or post commentaries in response to this article, see it online at http://www.annfammed.org/cgi/content/full/3/Suppl_1/530.

Key words: Practice-based research; ethics committees, research; institutional review boards; research subjects; legislation, medical; public policy

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Practice-Based Research Network Studies in the Age of HIPAA

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ABSTRACT

PURPOSE We wanted to explore potential effects of the Health Insurance Portability and Accountability Act (HIPAA) on research activities of practice-based research networks (PBRNs).

METHODS To understand the approaches PBRNs are using to advance their research while adhering to HIPAA standards, we combined a literature review, our experiences, and discussions with local HIPAA officers, PBRN researchers in the United States, and individuals involved in drafting HIPAA.

RESULTS HIPAA requires researchers to pay special attention to how they handle patients’ protected health information (PHI). For researchers working within PBRNs, which collect information from patients and health care professionals in multiple institutions, the HIPAA Privacy Rule presents additional challenges. PBRN researchers can obtain patient authorization to use PHI, but this process is difficult and may taint the findings of some research studies. Some institutions may allow patients to provide a blanket authorization for study recruitment. PBRNs additionally can collect only “de-identified” data (data with identifying information removed) or, with a data use agreement, can work with a limited data set. PBRNs that blend quality improvement and research can work with PHI, but the researcher and practices must enter into a business agreement. PBRN researchers may need to play active, educational roles in institutional privacy boards to facilitate their research.

CONCLUSIONS There are a number of ways for PBRN researchers to comply with HIPAA short of obtaining patient consent and authorization for every study. Careful planning and consideration of HIPAA issues during study design can go a long way toward reducing frustration later.


INTRODUCTION

The Health Insurance Portability and Accountability Act (HIPAA) was intended to improve and simplify the movement of individual patients’ protected health information (PHI) between health care professionals as well as to other entities that require the information, such as insurance companies. The act was written to accelerate the development of data standards for the transmission of health information, but it was quickly apparent that transmitting health information electronically presented hazards that required special attention. A pair of rules guide the implementation of HIPAA. The Health Insurance Reform: Security Standards, known as the Security Rule, describes standards for the security of electronic PHI. The Standards for Privacy of Individually Identifiable Health Information, generally known as the Privacy Rule, lays out specific processes to prevent potential abuse of electronically stored data, and especially abuse of easily linked PHI repositories. The requirements of the Privacy Rule have dominated the discussions of the legislation since its initial drafting and are the focus of this article.

Other authors have described some of the implications the HIPAA Privacy Rule has for general health services researchers and specialist researchers. These authors acknowledge that data collection schemes...
that provide valid data while meeting HIPAA privacy requirements can be challenging to develop. For researchers working within the complex environment of practice-based research networks (PBRNs), who intend to collect data from patients and health care professionals across multiple institutions, the Privacy Rule presents additional challenges.

Many PBRN studies are more like health services research than intervention-oriented randomized controlled trials because of the way in which PBRNs move research and data collection into the hands of practicing clinicians, at the point of care, and include all patients who meet selected criteria, not just those who consent to participate in a study. Such data collection plans require careful attention to comply with the Privacy Rule. PBRN researchers face additional challenges when they try to collect data about interventions at the practice level, often without individual patient consent—a design typical of translational research. Likewise, PBRN researchers must consider HIPAA concerns when designing approaches to patient recruitment. Although HIPAA was not intended to limit research, it does require special attention and compliance. In this article, we use several PBRNs’ experiences to explore ways in which the rules implementing HIPAA affect research conducted in PBRNs. We explain who needs to consider HIPAA, options for legally collecting and using PHI for research, and how a PBRN can determine its options in completing projects.

WHO NEEDS TO CONSIDER HIPAA?

The Privacy Rule applies to health care professionals and ancillary support operations that are considered “covered entities.” Covered entities are health care clearinghouses, health plans, and health care professionals who transmit or receive PHI in electronic form. For the purposes of this discussion, we assume that all practices or institutions within a PBRN, including the research core group, are covered entities. As we explain below, researchers may or may not be covered entities.

According to the Privacy Rule, covered entities must handle health information according to the 5 principles of fair information practices:

1. Notice: individuals (patients) have the right to know the existence and purpose of record-keeping systems.
2. Choice: patient information is (1) collected only with knowledge and permission of the individual, (2) used only in ways relevant to the purpose for which the data were collected, and (3) disclosed only with permission or overriding legal authority.
3. Access: individuals have the right to see their health records and to request adjustments in the record to ensure accuracy, completeness, and timeliness (this adjustment may be through changes to the record or additions to the record, based on the covered entities’ choice).
4. Security: individuals can expect that reasonable safeguards are in place for ensuring confidentiality, integrity, and availability of information.
5. Enforcement: violations may result in reasonable penalties and mitigation.

HIPAA does not prevent the use of PHI for quality improvement (QI) activities within the institution and its business partners. It does prevent the use of PHI for other purposes, even within a single institution, if patients have not authorized the use. Some examples of excluded activities are providing patient diagnoses and contact information to researchers for recruitment calls, even if the researchers are within the same institution, and sending dates of birth, and gender linked to diagnoses and dates of care to a PBRN central office for development of an age/sex/morbidity registry. HIPAA does not preclude informing individuals or their guardians of available services or even research projects as long as no PHI leaves the covered entity. For example, a primary care physician (not the research staff) can notify potentially eligible patients of a study involving free colorectal cancer screening. The regulations are designed to prevent the use of PHI for activities unrelated to clinical care without the patient’s expressed interest and consent. HIPAA thus places restrictions on the use of PHI that extends to research, unless the patient expressly agreed to a research use at the time the PHI was collected.

Receiving health information for the purposes of research does not, per se, make a researcher or the organization performing the research a covered entity under the Privacy Rule. As long as an organization’s sole use of PHI is for research and no clinical, billing, or administrative communications emanate from the research organization, the organization does not have to be considered a covered entity. In practicality, many research activities are tightly linked to other clinical care, and thus research organizations, such as universities or research arms of health maintenance organizations (HMOs), have elected to act like and consider themselves covered entities. HIPAA has established methods by which data may be obtained by researchers, but the HIPAA Privacy Rule does not specifically cover research and was not intended to interfere with research.

COLLECTING PHI FOR RESEARCH

All unauthorized disclosures of PHI are prohibited unless they are specifically permitted within the language of the Privacy Rule. This reverse approach to legislation—prohibited unless expressly permitted—creates fertile ground for varying interpretations of permissible approaches to research data collection.
This variety of interpretation is a major concern for PBRNs that deal with multiple institutional review boards (IRBs) and corporate attorneys, each of whom may have their own interpretation of acceptable research protocols. Often PBRNs have to develop study protocols that can gain approval across multiple IRBs without substantive changes that could potentially lead to serious compromises in subject recruitment and data collection. As part of an IRB application, researchers should engage in proactive discussions of how a proposed research activity meets all HIPAA requirements; these discussions can be helpful in overcoming more restrictive interpretations of the legislation.

Before further exploring HIPAA’s implications for PBRNs, it is useful to discuss the permitted choices researchers have for using PHI. There are 3 main options for collecting PHI for research: obtaining patients’ authorization (part of the consent process), using PHI without authorization (through a limited data set agreement or via data safety board [DSB] approval), and using de-identified data.

Option 1: Obtain Patients’ Authorization

Not considering the costs and trouble of obtaining patient consent, the straightforward way to collect and analyze PHI is with patient consent. When possible, obtaining patient consent is always the preferred method for collecting patient-level data. Even when patients have authorized the disclosure of their PHI for research, research organizations must still collect and store the data according to the requirements outlined by the Security Rule (not described here, but see Garner). Specific authorizations are now required by HIPAA, adding complexity to the basic consent process as discussed in detail below.

HIPAA Authorization

The Privacy Rule requires patients to provide specific, written authorization to disclose PHI. The patient must be fully informed about the use of the data to be collected and who will have access to the data. The following information concerning the collection and handling of PHI must be included as part of the authorization process:

- What types of data will be collected (eg, blood and urine test results, PRIME-MD [Primary Care Evaluation of Mental Disorders] survey data for psychological concerns, or results of specific imaging studies)
- The purpose of collecting the data (eg, to better understand approaches parents take to limit tobacco smoke exposure of their children or to evaluate this research project)
- Who will receive the data and the purpose for which the recipient will receive the data (eg, ABC Data Management Company for the purpose of data entry. Note that all recipients must be listed, and this listing is best done by role or group rather than by individual, in case specific individuals leave the study team. You do not have to list persons within your project team.)
- The length of time the data will be used, although it may be indefinite

Patients may revoke their authorization at any time. An example of an authorization form to disclose PHI for research is available online only as supplementary data in Appendix 1 at http://www.annfammed.org/cgi/content/full/3/Suppl_1/S38/DC1. Appendix 2, also available online only at http://www.annfammed.org/cgi/content/full/3/Suppl_1/S38/DC1, is an example of an authorization form to disclose PHI for recruitment into studies.

Obtaining Blanket Authorization for Study Recruitment

Many IRBs have created standardized forms to document patient authorization of 2 different types: authorization to disclose PHI for recruitment into studies and authorization to use or disclose PHI for participation in a research study.

When patients sign an authorization for patient recruitment, they are authorizing disclosure of specific information to researchers for the purpose of study recruitment and are granting permission to be contacted about that study. These forms were likely intended to provide authorization for a single research study and are used frequently in this manner by PBRN researchers. Researchers may instead want to develop more general authorizations, because authorizations can cover an extended or indefinite period of time. For a form to be used in this way, it must be written with more general terms so that the permission is not specific for 1 study. Individuals who agree to this global or blanket authorization must be provided with information on how to terminate the authorization.

Blanket authorization must be confined to a specific type of research, although the nature of this specificity is left up to each IRB. Disease-specific research fits easily within this framework (eg, authorization for future studies involving patients with hypertension, breast cancer, asthma, or back pain). The nature of primary care research makes such a blanket authorization difficult. A blanket recruitment authorization likely will not work for PBRN research that is not specific to 1 diagnosis, such as studies of practice process improvements that apply to multiple chronic diseases.

Option 2: Use PHI Without Authorization

In some instances the consent process can, in and of itself, invalidate the research outcomes. The Privacy Rule offers several other approaches to obtain PHI in
these situations. Use of PHI without patient authorization may be granted by IRBs or DSBs if obtaining consent is not practicable, risk to privacy is minimal, and the research cannot proceed without PHI. Practicable means capable of being done, or feasible; thus, situations wherein obtaining authorization is practicable may be considered not practical by many researchers. Obviously, the case for the potential benefit of the research versus the potential loss of privacy would need to be clearly stated to the reviewing authority. On occasion, a strong case that the consent process may change the research outcome and that benefits outweigh risks may be part of the “not practicable” argument as long as the criteria for using PHI without authorization are met. Widespread IRB acceptance of this argument is untested at this time.

PHI can also be used without patient authorization for protocol development, which means collecting information necessary to develop a grant application or research protocol. Most IRBs now require that a researcher submit a formal request to carry out this type of inquiry. (For an example of this type of form, see Appendix 3, available online only at http://www.annfammed.org/cgi/content/full/3/Suppl_1/S38/DC1.) Preliminary findings based on PHI obtained in this manner cannot be published. Finally, PHI of deceased people can be used without consent.

**Option 3: Use De-identified Data**

A final option, appropriate for many PBRN cross-sectional studies, is to create a “de-identified” data set. For a data set to be considered de-identified, all 18 identifiers listed in Table 1 must first be removed. In some instances, this removal process may not be adequate, such as in the case of extremely rare diagnoses where even at the state level, identification of the 1 or few patients with that diagnosis may be possible. In those instances, that piece of information could be removed from the data set or could be aggregated to a level where it is no longer identifiable to a specific person. It is unlikely that the loss of data at this level would adversely impact a PBRN study.

When collecting de-identified data, dates are the most commonly used data elements that create concerns. The Privacy Rule allows a date of birth to be recorded as a year, an age, or an age range. Year of birth or actual age cannot be used if the patient is older than 89 years; all patients older than this cutoff age must be grouped. The use of age ranges would appear to be an easy solution to this problem but can result in problematic data loss unless previous work has indicated the relationship of age to the study outcomes in question. In general, it is preferable to collect a year of birth or an actual age in years with a way, such as a check box, to indicate that a patient is older than 89 years. Although this solution appears straightforward, during clinical care, it can be difficult for clinicians or staff to write down a year of birth for some patients and to check a box for others. Electronic data collection systems can help in this regard. Dates of care are also a restricted data element and can cause considerable difficulty in longitudinal studies. We discuss options for addressing this problem below.

A data set that does not fit the Table 1 method of de-identification may also be used if a statistician certifies that the data could not be used to reidentify individuals. We discuss this approach further below.

The final approach to using de-identified data is the use of a limited data set, which includes dates. Collecting limited data sets requires that researchers have a data use agreement with the entity supplying the data, in this case, each practice or institution that owns the practice(s). This agreement must include wording that indicates that the researchers will not use the data to identify any study subject or contact any study subject. Although this approach is an enticing option under HIPAA, it can be time-consuming to get institutional HIPAA officers and lawyers to agree to supply limited data sets at this time, as the effects of the regulation are still being explored. Hopefully, with time, this option will become easier to invoke.

**APPRAOCHES FOR HIPAA COMPLIANCE IN PBRN RESEARCH**

In dealing with HIPAA regulations, PBRN researchers have a number of decisions and approaches to consider.
when designing a study. We present some general issues to consider when determining which approach works best for a given PBRN.

**Consent and Authorization Issues to Consider**

If patient consent is obtained, there are no restrictions on data elements that can be collected. HIPAA authorization forms, which describe what PHI will be collected and how it will be used, often run 3 pages in length, further burdening the already complex consent process. Attempts by IRBs to standardize HIPAA authorization forms may further complicate the process. For instance, some IRBs require the use of preprinted HIPAA authorization forms, on which the PHI to be collected and its use are selected from a long list. Our experience with these forms has been troublesome, as patients have difficulty understanding what parts of a lengthy HIPAA form are relevant to them; furthermore, because the HIPAA form is separate from the informed consent form, many people appear to have a difficult time relating the 2 forms to each other. We believe including PHI disclosure authorization as part of the study consent form is superior to using separate HIPAA authorization and consent forms. Combining these forms is clearly acceptable within the law but is not preferred by many IRBs and DSBs. We have not been successful at convincing all the IRBs and DSBs we work with that this approach is a superior one. Research concerning patients’ comprehension using the 2 options would be helpful.

Even without the extra burden of the HIPAA authorization, many PBRN directors believe clinicians and office staff cannot be expected to obtain patient consent within the regular work flow of a primary care office. The combination of potential ethical conflicts of patients’ primary care physicians asking them to participate in a study, the training requirements for individuals who obtain consent, and the time requirements to obtain full consent make obtaining consent an onerous task. The additional burden of HIPAA authorization, which can add considerably to an already complex research consent form, appears to further confirm this point.

Although obtaining patient consent and authorization solves data restriction problems, this process is time-consuming (and therefore costly) and more importantly dramatically changes which patients participate in a study. We found a large “consent bias” when consent was required for a survey similar to the National Ambulatory Medical Care Survey (NAMCS) within PBRN practices (unpublished data), as have others.7

Obtaining consent and authorization also changes the flow of care. Frequently, the process of care or the effectiveness of an intervention for an entire population is the research question of interest (see Glasgow et al8 for an example of such an intervention). Obtaining patient consent thus actually invalidates the results of the research by either creating a false care process or limiting potential participants. This phenomenon is true for cross-sectional studies using data collection at the point of care, such as the card studies popularized by the Ambulatory Sentinel Practice Network (ASPN),9 as well as many translation of research into practice (TRIP) activities wherein randomization often occurs at the practice level while outcomes are collected in a nested model at the patient level. HIPAA limits the nature and types of identifying data that can be attached to PHI in these types of studies, but with care, they are still feasible.

**Obtaining a Waiver of Patient Authorization**

PBRN studies are often epidemiologic in nature, and in epidemiologic studies, the consent process has been shown to markedly alter the research findings.5 Some PBRN studies might thus qualify for the waiver process. (An application for use of PHI through the waiver process is available in Appendix 4, available online only as supplementary data at http://www.annfammed.org/cgi/content/full/3/Suppl_1/S38/DC1.) This route has been successfully used by a number of researchers outside the PBRN arena, although it is likely to lengthen the IRB approval process. Researchers can furthermore expect a request of this nature to result in considerable variability in responses from one IRB to the next. These differing responses not only slow the research process, but may result in substantive changes in the research process from site to site, given the known variability among IRBs.11,12

**Obtaining Authorization for Recruitment**

Although obtaining patient authorization for study recruitment can be costly, it can pay off in the long term if the authorization is general enough (see blanket authorization, discussed above). The level of detail that must be communicated to patients about the potential research projects will vary from IRB to IRB. Researchers who have worked with this type of blanket authorization have generally found very high acceptance rates among patients, with only the occasional individual not granting this permission (personal communication, Mary Croughan, PhD, University of San Francisco, July 2, 2004).

If a PBRN considers this option, the practice or the network must develop a process for determining how to identify those individuals who provide their authorization to be contacted and must be able to update records for any individuals who rescind their authorization. These tracking requirements may make large health care organizations nervous about the time
must meet all HIPAA guidelines (ie, must either be de-identified, or be a limited data set with use agreements), but the QI data set is exempt from HIPAA. This process can make longitudinal data collection easier and allows the removal of PHI from the practice for the QI or patient care process. We and others have taken this approach with studies that focus on TRIP at the practice level. TRIP activities are QI activities, and we have used the QI characteristics to facilitate PHI exchange within these TRIP research projects. The expectation that the clinical activity supported by the business associate will continue beyond the specific research project is useful when considering this approach.

With this approach, a data use agreement for the research data should also be developed, and the PBRN should establish fire walls between any data held in the 2 databases. Our protocols require 2 completely separate teams of personnel from the PBRN: a data management team that helps practices implement a QI intervention, and a research team that receives de-identified data from the data management team for final evaluation and outcomes analysis (research). The practice and the data management team establish a business use agreement, and thus the data management team is a business associate of the practice. Sample language describing this system from a recent application is given in Table 2. A diagram of this separation, similar to that shown in Figure 1, may help communicate the clear distinction between the 2 teams. A similar 2-tiered system has been proposed to protect the usefulness of disease registries and the privacy of people listed therein.

Another approach to this process is for a third party, such as an Electronic Health Record vendor, to establish a business agreement with the PBRN practices, and for the vendor to then establish a research arrangement with the PBRN. The business partner may retain the linking number allowing a limited data set to be updated for research purposes over time. The PBRN thus obtains data at the practice level that it can use for outcomes studies without being able to track any data to a specific patient. Typically, the PBRN will work with the practices and vendor to establish study interventions, often supported by the Electronic Health Record. These interventions may include practice- or clinician-level feedback, patient-level reminders, case management activities, or other interventions (see Practice Partner Research Network [PPRNet]).

Table 2. Sample verbiage delineating the separation of the data management and research teams.

<table>
<thead>
<tr>
<th>Verbiage</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>The data management team will use the registry data to generate patient-activation materials on behalf of participating practices. The practice and data management team will establish a business use agreement and will outline the following data-sharing protocol. Participating practices and data management team will establish a HIPAA business associate agreement authorizing the data management team to serve as the registry data repository for quality improvement purposes. The agreement will outline the steps for de-identifying data, securing the data using appropriate computer technology, and destroying or returning the data after analyses are completed. The data management team will strip the data of all identifying information before sending them to the research team for evaluation purposes. The data management team will assign a temporary random-digit ID number for tracking purposes. Each time the data management team sends an updated data set to the research team, they will assign patients new temporary random-digit ID numbers, which will be destroyed as soon as the data management team transfers the new data set. The research team will delete the outdated data set and load the new data set each time a transfer is made.</td>
<td></td>
</tr>
</tbody>
</table>

HIPAA = Health Insurance Portability and Accountability Act; ID = identification.
For an example of a service agreement, adapted from the Pediatric Practice Research Group and Helen Binns, see Appendix 5, available online only as supplementary data at http://www.annfammed.org/cgi/content/full/3/Suppl_1/S38/DC1. A sample business agreement is available at the Web site of the Office for Civil Rights. If a PBRN is considering this option, it is wise to draft business use agreements for possible use and present the agreements to practices (or more specifically their legal counsel) for review long before study implementation.

Working With De-Identified Data

Tracking patient data for cleaning and verification, a frequent problem in all research, is made more problematic by HIPAA. No identifying number from the practice, such as a medical record number, may be transmitted without patient consent. HIPAA does however allow use of a reidentification tracking number. This method permits a number to be attached to the research data that only the practice can link back to the patient. Ensuring that practices maintain this linking number until a project is completed can be problematic. Electronic data collection can help alleviate the need for data cleaning if entry screens are programmed to guarantee complete collection (see the article on electronic data collection by Pace and Staton in this supplement). Unfortunately, it can be difficult to create practice-specific short-term tracking numbers within some electronic systems, particularly for data collection with a personal data assistant (PDA). Solutions to this problem are beyond the scope of this article.

When collecting de-identified data that require treatment intervals, it is acceptable to collect relative dates, such as the number of days between visits. This is not a practical solution for many PBRN studies wherein clinicians or office staff are collecting data and do not have time to convert dates to intervals. There are no easy solutions to this problem, although it may suffice for some IRBs or DSBs to shift dates forward or backward by a random number selected by the practice and unknown to the researchers. Once again, electronic systems may be helpful, as they can convert dates to intervals.

There is a common belief that HIPAA prohibits research personnel from performing chart reviews without patient consent. This belief is not correct, although whenever possible, it is wise to use office personnel for this activity. If the information collected during a chart review contains none of the identifiers listed in Table 1 and the practice allows research personnel access to records, data abstraction by research personnel is still allowed. This can be particularly important for practice-based interventions for which patient-level data are required and only available in the medical record, for instance, from control practices not using a disease-specific registry. Selecting a sample of patients' charts to review requires care as the practice may not transfer any PHI out of the office to the research team to assist with the randomization process. Once again, the use of a reidentification number as discussed above can assist with this activity.

As previously stated, a data set that does not fit the Table 1 method of de-identification may also be used if a statistician certifies that the data could not be used to reidentify individuals. It is unclear if any researchers have invoked this method. A PBRN would have trouble supporting this method at the practice level,
as it is highly likely that combinations of age, sex, and diagnoses could be uniquely matched within a practice population. Given the need to deal with the statistical concerns caused by clustering of data (ie, patients seen by individual clinicians within selected practices) that is typical of PBRN research,18 this method appears to offer little to PBRN researchers.

PBRN research is certainly more challenging in the era of HIPAA. Many tools and techniques used to help practices with the research process and ensure data accuracy must be carefully reviewed or revised. Patient consent has become more involved, and HIPAA authorization is now required for research designs that previously did not require consent. Even so, there are a number of ways for PBRN researchers to comply with HIPAA short of obtaining patient consent and authorization for every study. Careful planning and consideration of HIPAA issues during study design can go a long way toward reducing frustration later.

Covered health entities, IRBs and DSBs, and researchers may feel threatened and confused by alternative interpretations of the Privacy Rule. Some institutions have cited HIPAA as the reason for blocking particular activities outside the scope of this legislation, for instance, patient recruitment by study personnel located within the office. When this happens, it is often helpful to ask why the institution believes this activity is prohibited and to either educate individuals or find alternatives acceptable to both parties.

How a researcher presents planned data collection can influence how a protocol is viewed and whether it receives a favorable IRB review. Indicating how a data collection method is permitted within HIPAA guidelines, with appropriate references to the act, may be received differently than asking if a method is approved within HIPAA guidelines. For instance, chart abstraction by PBRN personnel on random patients within an office, without consent, will typically be considered a HIPAA violation, although it is permitted with appropriate safeguards. Face-to-face discussions with IRB and DSB personnel and the HIPAA officer of the PBRN’s host institution are valuable to explore options that meet the requirements of local authorities. Given the varied interpretations of HIPAA by institutional privacy boards, there is obviously no one best approach for PBRN research.

It is unclear whether over time PBRN practices and their host institutions will grow comfortable with HIPAA so that a new set of standard research-oriented activities can become routine, or whether the fear of patient complaints about privacy violations will further enshrine restrictive policies.

To read or post commentaries in response to this article, see it online at http://www.annfammed.org/cgi/content/full/3/Suppl_1/S38.

Key words: Practice-based research network; Health Insurance Portability and Accountability Act; informed consent; health services research

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ABSTRACT

PURPOSE This article reviews examples of and experience with longitudinal research in family medicine. The objective is to use this empirical information to formulate recommendations for improving longitudinal research.

METHODS The article discusses 3 longitudinal studies from the Nijmegen academic family practice research network: 1 on the prognosis of depression and 1 each on the prognosis of and outcomes of care for type 2 diabetes mellitus. The Nijmegen network has recorded all episodes of morbidity encountered in Dutch family medicine since 1971 in a stable practice population. This network’s experience is evaluated to identify lessons that may help other practice-based research networks (PBRNs) in pursuing longitudinal research.

RESULTS In terms of external conditions (conditions related to the general setting), the stability of a population and a high level of continuity of care substantially enhance the ability to perform longitudinal research. In terms of internal conditions (conditions related to the PBRN), motivation of family physicians and their staff to conduct ongoing data collection, and their ownership of the data are key for success. Other critical internal conditions include standardization of data; collection of data by clinician-friendly means; training of family physicians and their staff in data collection, as well as meetings for discussion of this task; provision of feedback to practices on the research findings; use of standard procedures to promote adherence to data collection; availability of facilities for regular measurement of patients’ health status or chart review; and use of mechanisms for tracking patients who leave the practice area.

CONCLUSIONS Insight from existing experience suggests that longitudinal research can be enhanced in PBRNs. The best way forward is to build longitudinal data collection by drawing on lessons from successful studies. Primary care research policy should advocate for a role of longitudinal research and stimulate its development in PBRNs under favorable population circumstances.
care) form the basis of FPs’ preventive and therapeutic interventions.\(^1\)\(^2\) To provide care with an eye to patients’ futures, clinicians must have evidence on the long-term effects of preventive and therapeutic interventions.\(^3\) This need is the impetus behind longitudinal research.

Unfortunately, longitudinal research is underappreciated, and the conditions of care often pose challenges to such research: health care systems connect patients and providers for episodic rather than ongoing care, while the geographic mobility of patients and FPs hampers the establishment of lasting working relationships. As a consequence, the research infrastructure needed to study health problems in their long-term context is poorly developed.

**Primary Care Practice-Based Research Networks**

Primary care practice-based research networks (PBRNs) have emerged as the infrastructure for research in family medicine.\(^4\)\(^5\) PBRNs can tap into the continuity of patient care and extend the time window of research beyond the few years usually covered by research projects. The long-term natural history of disease and the outcome of care are essential pieces of information in assessing the effectiveness of family practice.

PBRNs are driven by the research interests of practitioners, resulting in their ownership of research. This ownership enhances a long-term commitment to data collection. But consistent data collection over time and ongoing adherence to study protocols also require ensuring that data are collected in a methodologically rigorous way; furthermore, linking PBRNs to a research center or university\(^5\)\(^6\) is particularly important for longitudinal research. Models of successful research in family practice clearly show the possibility of training of FPs and their staff in data collection and introducing a scientific esprit de corps in this setting.\(^7\)\(^-\)\(^1\(^1\)

**Structuring Longitudinal Data in Primary Care**

PBRNs constitute a multicenter research setting, and standardization of data and terminology within networks is therefore essential. Standardization is particularly important for longitudinal research: data must not only be consistent across different study sites, but even more important, must be consistent over time.

To structure data longitudinally, information on visits and contacts must be organized into “episodes of illness”\(^9\)\(^12\) that can in turn be linked over time to individuals. A first prerequisite is to classify each health problem encountered during practice visits as either a new problem or part of an established problem, and to link the data from multiple practice visits into episodes of illness. The International Classification of Primary Care (ICPC)\(^1\)\(^2\) offers a framework to structure episodes, and this framework can be used even without concomitant use of the ICPC classification for recording relevant information, such as physician contact, diagnosis, and diagnostic and therapeutic procedures. This approach is used, for example, in the Nijmegen database,\(^5\) from which a number of examples are presented below.

Using both ICPC components has advantages, however, as it helps to further structure the clinical information. In Dutch family practice, for example, the recording of information has been made easier because the ICPC has been used to structure the electronic medical record; the result is a user-friendly way of collecting and recording data under routine conditions of care. In particular, for disease-specific research, ICPC offers diagnostic criteria\(^1\)\(^1\) that are applicable under primary care conditions.

A second prerequisite for structuring longitudinal data is to assign episodes to individual patients, for example, through a unique personal identification code. The process can be refined by adding patients’ socioeconomic characteristics and by classifying individuals living in the same household as families. This approach is likewise facilitated in Dutch databases because the health care system works with FPs’ personal lists of patients, and whole families usually register with the same FP.

**EXAMPLES OF LONGITUDINAL STUDIES**

Below, 3 examples of longitudinal studies from the Nijmegen academic family practice research network\(^5\)\(^7\)\(^-\)\(^1\(^1\) are discussed to illustrate a number of challenges in longitudinal research: (1) ensuring that the database can bridge time, (2) assessing how representative the data are of family practice at large, (3) maintaining scientific quality control of the data, and (4) assessing how quality and consistency of patient care may influence research results.

**Research Setting**

The Nijmegen academic family practice research network was founded in 1971 in 4 practices to record all episodes of morbidity for which patients consulted FPs (including those for diagnoses made by specialists after referral) and cause of death among these patients. This recording, which takes place in a stable practice population of approximately 12,000 people, has continued ever since; consequently, the data set that has developed enables the tracking of individuals’ medical histories for more than 30 years. Since 1986, the 4 practices, together with 5 other practices in the region, have been recording all data related to the process and outcomes of care among patients with chronic diseases (diabetes mellitus, hypertension, and asthma and chronic obstructive pulmonary disease) and have been giving practices and FPs structured feedback on these measures.\(^8\)

The database is a key component of the Nijmegen family medicine research program of longitudinal research among patients with chronic diseases. The impetus for establishing this database was the need to access
previously unavailable empirical morbidity data from family practice, at the time of founding of the Department of Family Medicine at Nijmegen University. At that time, the research interest was in the development of morbidity in families and over generations; of note, stability of the practice population and continuity of care were such self-evident features that they were taken for granted. In hindsight and with evidence of continued stability of this population at a time of increasing geographic mobility in the Dutch population, no better location could have been chosen for longitudinal data collection.

A number of measures have been taken to ensure consistent recording and classification of information in the database over time:

- Since founding of the network, the classification for morbidity has been unchanged; conditions are classified using the Dutch translation of the E-book.
- All FPs in the network meet regularly to discuss and compare their approaches to registering patients and classifying conditions; in the event of disagreement, consensus is sought and formulated in the registration rules. The comparability of FPs' performance is checked using case vignettes. These meetings remain important despite the lengthy experience of most FPs in the network and their use of the same classification.
- New FPs joining the practices are trained in the use of the classification and the registration rules.
- Practice assistants are trained and regularly supervised in the assignment of unique patient- and family-identifying codes, and in the entry of patients' social and demographic information.
- In every practice, practice assistants ensure that recorded data are transported from the practice to the central database.

All patients on the practices' lists are informed of the use of the database for research and asked to provide written consent. If a patient leaves the practice, the patient's new address and the name and address of the patient's new FP are recorded to enable future contact.

Example 1: Depression Recurrence Among Family Practice Patients

Depression is a common chronic condition in family practice for which long-term treatment with antidepressant medication is recommended to prevent a recurrence. As this recommendation is based on research among patients referred for psychiatric care, the aim of the study undertaken with the Nijmegen database was to establish the incidence of recurrence after a first episode of depression among patients treated in family practice.

In looking for an alternative to a long-term prospective study, the investigators considered analyzing data from the Nijmegen family medicine database, which makes it possible to identify patients in whom depression was diagnosed up to 20 years earlier. The investigators therefore undertook a historic cohort study (described in a later section). From the database, they enrolled all patients who had experienced a first episode of depression between 1971 and 1986. Selection of this time period allowed for a follow-up of at least 10 years after the first episode.

A major challenge was to determine whether all patients had had major depression. For the study findings to be relevant, it was essential that the condition was depression as it is currently understood and defined. It was not possible to assess the criteria used to make the diagnosis through a chart review because FPs only occasionally recorded such information. For that reason, the investigators used a proxy of diagnostic accuracy of depression by the FPs, assessed through psychiatric interviews with patients with recently diagnosed depression. This evaluation showed that in most cases, the episode had fulfilled the diagnostic criteria of major depression according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. To assess the current health status and quality of life of patients enrolled in the study, all were sent a set of questionnaires.

The study found that 60% of patients in whom depression had been diagnosed did not have a recurrent episode in the 10 years thereafter—a rate higher than expected based on studies in psychiatry. Results obtained with the questionnaires showed that depression nonetheless continued to have a major adverse impact on patients' quality of life years later, even with no recurrence.

Example 2: Cardiovascular Complications Among Patients With Diabetes Mellitus

The aim of the second study using the Nijmegen database was to assess the risk of cardiovascular complications among patients with type 2 diabetes mellitus being treated in family practice. At the time of the study in 1989, this outcome was largely undocumented.

The first challenge of this study was to determine the medical history of patients since the diagnosis of diabetes. Again, the investigators formed a historic cohort, this time one of all patients in the database with diabetes mellitus diagnosed between 1971 and 1989. The complete medical history after diagnosis had been recorded and coded routinely in the database for all of the patients. The data therefore allowed a follow-up from the time of diagnosis until (1) the end of the observation period in 1994, (2) death of the patient, or (3) departure of the patient from the practice. With this approach, 265 patients were enrolled, and the maximum observation time since diagnosis was 23 years. For each diabetic patient (case), the investigators selected a nondiabetic patient (control) matched for age, sex, and social class who received care from the same FP.

The second challenge was determining whether all
patients selected truly had diabetes mellitus. This methodologic question was particularly important because in 1985, shortly before the design of the study—but in the middle of the historic observation period—the diagnostic criteria for diabetes mellitus changed. The question was therefore whether patients given a diagnosis of diabetes by their FP, particularly before 1985, had diabetes mellitus according to the 1985 criteria.

The investigators undertook a chart review of all patients enrolled. Using all written notes and laboratory reports, they established that more than 95% of the cases fulfilled the reference criteria released in 1985. A comparison of cases fulfilling these criteria with their matched controls demonstrated elevated risks of cardiovascular morbidity and mortality among the cases, and consequently a poor prognosis of diabetes mellitus type 2 in the family practice setting.

Example 3: Diabetes Care in Academic Family Practices
In a follow-up of the analysis of the diabetes cohort, the outcomes of treatment of diabetes mellitus in family practice were studied and compared with external criteria.

An audit-and-feedback system was introduced in the network in 1992 to improve diabetes care. Using the database, the investigators assessed process of care and outcomes of care in all patients with diabetes mellitus 1 year later (1993) and again 7 years later (1999). They compared these measures with those outlined in the Dutch College of General Practitioners' guidelines for diabetes mellitus and with those of a state-of-the-art randomized clinical trial.

Between 1993 and 1999, outcomes improved substantially. By 1999, blood glucose levels were adequately controlled in 52% of patients, blood lipid levels in 83%, and systolic and diastolic blood pressure in 54% and 66%, respectively. These percentages were in the same order as those achieved under the conditions used in the randomized trial.

The challenge in this study was the interpretation of the findings. The investigators concluded that high-quality diabetes treatment was feasible in family practice. But given the self-selection of FPs in the network and their academic setting, the findings were not generalizable to unselected FPs, whose diabetic patients had poorer outcomes.

External Conditions
External conditions that are favorable for longitudinal research include stability of the population and continuity of care. In principle, every family practice database holds longitudinal data from patients, but the validity of those data is determined by how long patients remain in the practice. As previously noted, the population served by the Nijmegen academic family practice research network has remained very stable over time. The Dutch health care system, with its high level of continuity of care between patients and FPs, offers more favorable conditions than the US system for longitudinal research.

Internal Conditions
In planning a PBRN for longitudinal data collection, it is logical to choose a setting that offers optimal external conditions for such research, but the internal conditions that the PBRN can create and control are as important. First among these conditions is to secure the ongoing commitment of FPs and their staff to longitudinal data collection. Ownership of data is crucial to such a commitment. In addition, success breeds success, and longitudinal data collection should be encouraged as an extension of successful PBRN activities. Other conditions that PBRNs can control include the following:

- Standardization of data between FPs and between practices, and over time
- Integration of data collection for research with that for patient care in an FP-friendly manner
- Training of FPs, other physicians, and staff in the use of classifications and the rules for data collection
- Provision of meetings for FPs and other physicians in the network to discuss and compare data collection, and to give feedback from the collected data
- Use of standard procedures to promote adherence to data collection
- Provision of facilities for regular measurements of patients' health status or chart reviews
- Use of mechanisms for tracking patients who leave the practice area

BUILDING LONGITUDINAL DATABASES AND QUALITY OF RESEARCH DATA
When building a longitudinal database and planning for high-quality longitudinal research, PBRNs must consider both external conditions (ie, those related to the general setting) and internal conditions (ie, those related to the network itself).

DESIGN OF LONGITUDINAL STUDIES
Approaches When Working With Existing Databases
In the examples given above of longitudinal studies conducted with a database, patients were enrolled because of a defined health event in their medical past—in example 1, a first episode of depression; in example 2, a diagnosis of diabetes mellitus—and from that event onward, a sequence of health events (diagnoses) was constructed. This design is called a historic cohort study. Although all events studied occurred and were recorded before the time of study, it is important...
to emphasize that the recording was done prospectively. In addition, FPs who performed the recording did so without knowledge of later studies that would use the data. In these respects, a historic cohort study differs essentially from a retrospective study.

In example 2, the incidence of cardiovascular complications in patients with diabetes mellitus (cases) was compared with that in matched nondiabetic patients (controls). In this way, a case-control approach was built into the historic cohort study. In example 3, the outcomes of care among a cohort of patients with diabetes mellitus (assessed from their current health status) were compared with those from external sources. This study is an example of outcomes research.

When working with an existing database, these 3 approaches—historic cohort studies, case-control studies, and outcomes research—are the ones most commonly used for longitudinal research.

Alternate Approaches
An alternate approach to longitudinal research is to use a randomized controlled trial (RCT) or other interventional study as the starting point for longitudinal observation. For example, the 1986 extension of the Nijmegen database with follow-up data on chronic diseases was based on the follow-up of an RCT of cardiovascular prevention. Investigators must keep in mind when using this approach, however, is the informed consent of patients and practitioners, which is usually given for a study that ends after a finite period. Data collected from that time forward will as a rule relate to the patients’ courses under usual care, as it is only occasionally possible to continue the experimental study conditions for a longer period. Like longitudinal studies that use existing databases, these studies must also meet the conditions of stability of the population and rigorous collection of follow-up data.

ISSUES IN LONGITUDINAL RESEARCH
Unbiased Observation
As the emphasis in longitudinal research is on descriptive studies, investigators should take into account the methodologic limitations of this research, such as difficulty in achieving unbiased observation in some cases. Particularly when studying outcomes of care, confounding by clinical indication interferes with unbiased observation. This phenomenon has recently been analyzed in depth in the case of hormone replacement therapy (HRT). Cohort analyses documented reduced rates of cardiovascular events among HRT users, but RCTs later demonstrated elevated rates of such events in this group. The likely explanation for this contradiction was that practitioners had suspected that HRT might have cardiovascular adverse effects and therefore restricted use of this therapy to women with low cardiovascular risk—an example of confounding by clinical indication.

Several strategies can be used to minimize bias in longitudinal studies. One strategy would be to include all patients with the problem being studied in the practice database—the full cohort. This is the strength of the studies described in examples 1 and 2. In example 3, however, which describes a study that excluded diabetic patients who died during the observation period, the inclusion of these patients might have yielded different study results. For this group in particular, tight metabolic and risk-factor control would have been important for optimizing outcomes, but also least likely to have been achieved—a fact that might have contributed to these patients’ deaths. Another strategy would be to include, in addition to the standard social and demographic data of patients, detailed clinical background data such as comorbidities and cotreatments, risk factors, or family medical history. These are the thick and rich descriptive data that family practice databases can provide.

Influence of Quality of Care
The ultimate goal of investing in the research infrastructure of PBRNs is to optimize patient care. But long-term analysis of the course of disease usually shows its course under routine clinical care and, in this way, quality of care influences the research. Studying the illnesses and diseases of patients over time requires optimal or at least consistent patient care, just as research requires high-quality and consistent data. This issue is particularly of concern in longitudinal research because deviations from classification criteria or care protocols, or selective participation and dropout accumulate over time, and even when these events occur at a modest rate, their cumulative effect can be substantial.

Generalizability of Research Results
Participation of FPs in clinical research is inevitably a process of self-selection; furthermore, the more strenuous the research efforts, the stronger this process of self-selection. Longitudinal research requires an ongoing commitment to research and, for that reason, PBRNs involved in this type of research in particular can be expected to represent a self-selected group of FPs.

Investigators must keep sight of the implications of self-selection for research findings. In study example 3, a study of outcomes of diabetes care, the focus of research was the performance of the FPs, for example, their adherence to protocols for care. In this case, self-selection will be a major issue, and the participating FPs will not represent FPs at large. But the focus of research in the studies in examples 1 and 2 of the prognosis of depression and diabetes, respectively, was patients and their health problems. Self-selection of FPs should be much less of a prob-
lem, as FPs care for unselected patients representing the local community population. For that reason, longitudinal data collection in PBRNs leads to generalizable findings for family medicine when the focus of research is on the unselected patient population. In other words, PBRNs that have been planned under conditions that favor continuity of care still represent family practice at large. This factor should encourage the discipline of family medicine in strategically planning longitudinal databases.

CONCLUSIONS AND RECOMMENDATIONS

PBRNs provide a solid basis for ongoing research in family practice that can capitalize on FPs’ ongoing commitment to the care of their patients over time. Longitudinal analysis of the clinical course of disease is essential to support clinical decision making that is focused on the long-term perspective. Family practice records contain a rich multitude of patient-related clinical data collected over longer periods, which in principle can be a wealth of data for researchers. The historic cohort study makes it possible to bridge a substantial time frame in the follow-up of patients. Linking longitudinal databases to PBRNs is more efficient than creating new study cohorts, and the data collected in such databases are prospective in nature.

For longitudinal databases to be scientifically valid, it is important to invest in the scientific activities of PBRNs, such as training FPs and staff in data collection and use of classification systems. Self-selection of the FPs in PBRNs has considerable implications for research on quality of care, but is less influential for research on disease or clinical course over time. As long as PBRNs care for unselected populations, longitudinal studies will represent primary care at large, and this fact allows for strategically planning PBRNs for longitudinal research under conditions favoring continuity of care.

Internationally, family medicine has developed a comprehensive classification system on which data collection can be based. This system permits introduction of clinician-friendly scientific criteria in family practice, and there is strong evidence that it is possible and relevant to engage FPs in such a process. This supports the further development of a research culture in family medicine with a longitudinal perspective. It is the best basis on which to advocate for better research funding of studies that span long periods of time.

To read or post commentaries in response to this article, see it online at http://www.annfammed.org/cgi/content/full/3/Suppl_1/S546.

Key words: Longitudinal studies; PBRNs; primary health care; family practice; research design; databases; long-term care; historical cohort studies

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Multilevel Modeling and Practice-Based Research

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ABSTRACT

PURPOSE The health care system in the United States is inherently hierarchical. Patients are "nested" within physicians who in turn are "nested" within practices. Much of the research data gathered in practice-based research networks (PBRNs) also have similar patterns of nesting (clustering). When research data are nested, statistical approaches to the data must account for the multilevel nature of the data or risk errors in interpretation. We illustrate the concept of multilevel structure and provide examples with implications for practice-based research.

METHODS We present a selection of multilevel (hierarchical) models and contrast them with traditional linear regression models, using an example of a simulated observational study to illustrate increasingly complex statistical approaches, as well as to explore the consequences of ignoring clustering in data. Additionally, we discuss other types of outcome data and designs, and the effects of clustering on sample size and power.

RESULTS Multilevel models demonstrate that the effects of physician-level activities may differ from clinic to clinic as well as between rural and urban settings; this variability would be undetected in traditional linear regression approaches. Study conclusions differed when the data were analyzed with multilevel methods compared with traditional linear regression methods. Clustered data also affected sample size; as the intraclass correlation increased and the patients per cluster increased, the required number of patients increased dramatically.

CONCLUSIONS Recognizing and accounting for multilevel structure when analyzing data from PBRN studies can lead to more accurate conclusions, as well as offer opportunities to explore contextual effects and differences across sites. Accommodating multilevel structure in planning research studies can result in more appropriate estimation of required sample size.


INTRODUCTION

Many studies conducted in practice settings collect patient-level data (such as blood pressure measurements) as the dependent variable. Usually, such data have a hierarchical structure, with patient-level measures clustered (nested) within physicians and multiple physicians clustered within the same practice. (For definitions of the statistical terms we use in this article, see Table 1.) When analyzing such data, it is important to recognize hierarchical/multilevel structure and account for similarities among individuals within groups.1-6 Traditional statistical methods, such as logistic or linear regression analysis, assume that observations are uncorrelated; however, in the case of hierarchical/multilevel data (also called clustered or nested data), these assumptions are unrealistic. Individual observations (eg, patient-level blood pressure measurements) that are clustered within a higher-level unit share a common environment and may be more similar than observations from individuals in different higher-level units. In health care settings, patients treated by a particular clinician receive care in a common treatment setting that is influenced by clinician characteristics.
Table 1. Glossary of Terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multilevel/hierarchical/clustered/nested data</td>
<td>Data that have some inherent group membership (eg, students within schools, patients with clinics) or hierarchical structure</td>
</tr>
<tr>
<td>Multilevel models/hierarchical linear models (HLMs)</td>
<td>A type of statistical procedure belonging to the class of general linear models, adapted for analysis of clustered data</td>
</tr>
<tr>
<td>Analysis of variance (ANOVA)</td>
<td>A statistical procedure used to compare means of a continuous outcome variable for more than 2 groups, classified by 1 or more categorical variables; for example, comparison of patient scores on a functional health survey for 4 nonoverlapping diagnostic groups by 2 sex categories</td>
</tr>
<tr>
<td>Analysis of covariance (ANCOVA)</td>
<td>An extension of ANOVA in which the means of a continuous outcome variable are compared across groups, as described above, adjusting for 1 or more continuous covariates; for example, comparison of patient scores on a functional health survey for 4 nonoverlapping diagnostic groups, adjusted for age</td>
</tr>
<tr>
<td>Fixed effects</td>
<td>A condition in which the levels of a factor include all levels of interest to the researcher (eg, sex: male or female)</td>
</tr>
<tr>
<td>Intraclass correlation coefficient (ICC)</td>
<td>A measure that describes the extent to which individuals within the same group are more similar to each other than they are to individuals in different groups</td>
</tr>
<tr>
<td>Random effects</td>
<td>A condition in which the levels of a factor represent a random sample of all possible levels (eg, clinics)</td>
</tr>
<tr>
<td>Linear regression analysis</td>
<td>Simple linear regression analysis assesses how a continuous outcome variable (or dependent variable) changes per unit change in a predictor variable (or independent variable). Multiple linear regression analysis assesses the relationship between 1 dependent variable and more than 1 independent variables.</td>
</tr>
<tr>
<td>Residual variance</td>
<td>The remaining variance in the outcome variable (dependent variable) after accounting for all predictors (independent variables) and random effects of interest</td>
</tr>
</tbody>
</table>

and philosophy, and that may differ from one clinician to another; clinicians within the same practice share a common practice environment that is influenced by the practice setting and other characteristics. Ignoring group membership can result in erroneous conclusions, as demonstrated in studies from educational settings.7 The choice of analytic methods for clustered data can have major implications for research by practice-based research networks (PBRNs), which almost always involves sampling patients from multiple physicians and clinics. Investigation of the effects of macrolevel characteristics on individuals has been carried out in educational and organizational research but is relatively new in health research.1,9

Most statistical procedures involve understanding sources of variance among experimental units (eg, people). Traditional approaches (ie, ordinary least squares [OLS]) such as analysis of variance and multiple linear regression analysis ignore dependencies within groups, but advances in analytic approaches (general linear mixed models, hierarchical linear models, random regression modeling) and computing software10,11 can account for the multilevel structure of the data and also for the random variation associated with sampling higher-level units, such as physicians or practices.

In a simple 2-level model, the sources of variance are within-groups and between-groups. Using a PBRN context with patients sampled from clinics, the total variation in patient outcomes can be partitioned into 2 variance components: within-clinics variance (ie, variance among patients in the same clinic) and between-clinics variance (ie, variance between patients in different clinics). When patients within groups are very similar to each other, we have less information than we would have from the same number of patients obtained in a simple random sample (ie, an unclustered sample). An important measure that describes these dependencies in the data is the intraclass correlation coefficient (ICC); this statistic measures the extent to which individuals within the same group are more similar to each other than they are to individuals in different groups. We will explain this measure more fully in the next section. Issues around violations of distributional assumptions such as nonindependence of measures have long been recognized, but technical advances that make such complex analytic methods accessible are fairly recent.8-13

In this article, we illustrate the concept of multilevel (hierarchical) structure and analytic approaches, using a specific example from the health field with data simulated to maximize clustering effects, and we contrast multilevel methods with traditional methods. We include an overview of modeling approaches for studies with continuous outcomes and hierarchical structure. We cover 2-level models in detail, illustrating the conceptual ideas behind multilevel approaches and contrasting them with traditional methods. The analyses progress from simple to complex, with 2 traditional models and 5 multilevel models (also called hierarchical linear models [HLMs]). The models described below can be adapted or extended to cover most research designs common to PBRNs. We include an additional statistical model for studies with dichotomous or binary outcomes and briefly discuss other applications. Finally, we address issues pertaining to power and sample size for clustered data, and give some examples.

ILLUSTRATION OF TRADITIONAL AND MULTILEVEL ANALYSES FOR A PBRN STUDY

We use a hypothetical observational PBRN study and a simulated database to illustrate the results obtained with different traditional and multilevel models in a context with large between-clinic differences. The purpose of the study was to examine the effect of time spent by physicians giving advice to patients regarding alcohol consumption on their alcohol consumption during 1 year. The data set consists of 500 patient-level observations. Patients were randomly sampled from 1 physician in each of 5 clinics (100 patients per physician), with 3 clinics located in an urban area and 2 in a rural setting. The dependent variable, a continuous
variable, was the number of alcohol-free weeks per patient during 1 year. The independent variables included the number of hours per year of physician advice each patient received (a patient-level variable) and clinic location, classified as urban or rural (a clinic-level covariate). The 500 patients in this study reported an average of 14.61 (SD, 2.12) alcohol-free weeks during the past year (Table 2). Figure 1a illustrates the distribution of number of alcohol-free weeks by physician advice over all clinics in a scatter plot.

Traditional Models

HLM Model 1: Random-Effects Analysis of Variance

The simplest multilevel model is a 1-way analysis of variance (ANOVA) with clinic random effects; the assumption is that we have sampled from a population of clinics (just as we typically sample from a population of patients). In contrast to the overall mean and SD of number of patient alcohol-free weeks reported in Table 2, this model estimates the mean number of alcohol-free weeks (\(y_{ij}\)) for each clinic and decomposes the total variance in that number (\(y_{ij}\)) into the between-clinic (level-2) and within-clinic (level-1) variance components, that is, variability due to differences in the mean number of alcohol-free weeks for the 5 clinics and variability in the number of alcohol-free weeks for patients within the same clinic. (A detailed description of this statistical model and the others we discuss is given as supplementary data in the Supplemental Appendix, available online only at http://www.annfammed.org/cgi/content/full/3/Suppl_1/S52/DC1.)

The ICC reflects the extent to which patients within the same clinic are more similar to each other than they are to patients in different clinics. It is the proportion of the total variance that is due to differences among clinics. ICCs are very important in planning studies and analyzing data that have hierarchical structure, which is common to most practice-based research. Obviously, the degree to which individuals within a practice are more similar than individuals in different practices depends on the outcome of interest, as well as other factors, and will vary from one study to another.

The results from applying the random-effects ANOVA model to the alcohol data set are given in Table 2 (see HLM Model 1). Note that the variance is now decomposed into a between-clinic variance (1.76) and a within-clinic (residual) variance (1.41). The estimated ICC indicates that the ratio of the between-clinic variance to the total variance is about 55%, calculated as ICC = 1.76/(1.76 + 1.41), suggesting that patients within clinics are more similar to each other than to those at other clinics. (ICC ranges from 0 to 1 [or 0% to 100%], with higher values representing stronger clustering effects.)

REG Model 1: Traditional Linear Regression Model 1

The most commonly used analytic approach to our hypothetical problem would be the simple linear regression model (online Supplemental Appendix, see REG model 1). This model is essentially a patient-level model, but one can visualize it as a 2-level model with fixed effects, that is, the mean number of alcohol-free weeks among patients without any physician advice—intercept \(\beta_0\)—is the same for all clinics, and the effect of physician advice on patient alcohol-free weeks, per unit of time spent—slope \(\beta_1\)—is also the same across all clinics.
Table 2. Study Results Obtained With Differing Models

<table>
<thead>
<tr>
<th>Description of the data</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>y&lt;sub&gt;ij&lt;/sub&gt; Number of alcohol-free weeks in 1 year for patient i from clinic j</td>
<td>14.61 (2.12)</td>
<td>8.7-19.1</td>
</tr>
<tr>
<td>x&lt;sub&gt;ij&lt;/sub&gt; Total hours of physician advice per year for patient i from clinic j</td>
<td>0.56 (0.30)</td>
<td>0.002-1.23</td>
</tr>
<tr>
<td>w&lt;sub&gt;j&lt;/sub&gt; Urbanicity: urban = 1; rural = 0</td>
<td>0.6</td>
<td>0-1</td>
</tr>
</tbody>
</table>

| Notation                                                                                   |                  |             |
| i                                                                                         | Indexes patients within a clinic | 1-100       |
| j                                                                                         | Indexes clinics   | 1-5         |

HLM model 1: random-effects ANOVA model

<table>
<thead>
<tr>
<th>Fixed effects</th>
<th>Estimate&lt;sup&gt;*&lt;/sup&gt;</th>
<th>SE</th>
<th>t</th>
<th>df</th>
<th>Pr &gt; t</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\gamma_0) (grand mean)</td>
<td>14.61</td>
<td>0.79</td>
<td>18.46</td>
<td>499</td>
<td>.000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Random effects</th>
<th>Estimate&lt;sup&gt;*&lt;/sup&gt;</th>
<th>Pr(H&lt;sub&gt;0&lt;/sub&gt;: (\tau = 0))</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\tau_0) (between-clinic variance)</td>
<td>1.76</td>
<td>.000</td>
</tr>
<tr>
<td>(\sigma^2) (residual variance)</td>
<td>1.41</td>
<td></td>
</tr>
</tbody>
</table>

REG model 1: traditional linear regression model 1†

<table>
<thead>
<tr>
<th>Fixed effects</th>
<th>Estimate&lt;sup&gt;*&lt;/sup&gt;</th>
<th>SE</th>
<th>t</th>
<th>Pr &gt; t</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\beta_0) ((\gamma_1)) – slope</td>
<td>1.31</td>
<td>1.23</td>
<td>1.07</td>
<td>.345</td>
</tr>
<tr>
<td>(\beta_1) ((\gamma_0)) – intercept</td>
<td>13.87</td>
<td>1.19</td>
<td>11.69</td>
<td>.000</td>
</tr>
<tr>
<td>(\sigma_2) (residual variance)</td>
<td>2.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HLM model 2: random-intercept model

<table>
<thead>
<tr>
<th>Fixed effects</th>
<th>Estimate&lt;sup&gt;*&lt;/sup&gt;</th>
<th>SE</th>
<th>t</th>
<th>df</th>
<th>Pr &gt; t</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\gamma_1) (slope)</td>
<td>2.38</td>
<td>1.05</td>
<td>2.26</td>
<td>498</td>
<td>.024</td>
</tr>
<tr>
<td>(\gamma_0) (average intercept)</td>
<td>13.27</td>
<td>1.30</td>
<td>10.24</td>
<td>4</td>
<td>.000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Random effects</th>
<th>Estimate&lt;sup&gt;*&lt;/sup&gt;</th>
<th>Pr(H&lt;sub&gt;0&lt;/sub&gt;: (\tau = 0))</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\tau_0) (variability in clinic intercepts)</td>
<td>3.47</td>
<td>.000</td>
</tr>
<tr>
<td>(\sigma^2) (residual variance)</td>
<td>1.65</td>
<td></td>
</tr>
</tbody>
</table>

HLM model 3: random-coefficients model

<table>
<thead>
<tr>
<th>Fixed effects</th>
<th>Estimate&lt;sup&gt;*&lt;/sup&gt;</th>
<th>SE</th>
<th>t</th>
<th>df</th>
<th>Pr &gt; t</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\gamma_1) (average slope)</td>
<td>2.96</td>
<td>0.89</td>
<td>3.31</td>
<td>4</td>
<td>.040</td>
</tr>
<tr>
<td>(\gamma_0) (average intercept)</td>
<td>12.80</td>
<td>1.32</td>
<td>9.74</td>
<td>4</td>
<td>.000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Random effects</th>
<th>Estimate&lt;sup&gt;*&lt;/sup&gt;</th>
<th>Pr(H&lt;sub&gt;0&lt;/sub&gt;: (\tau = 0))</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\tau_0) (variability in intercepts across clinics)</td>
<td>10.71</td>
<td>.000</td>
</tr>
<tr>
<td>(\tau_1) (variability in slopes across clinics)</td>
<td>4.74</td>
<td>.000</td>
</tr>
<tr>
<td>(\tau_{11}) (covariance between intercept and slope)</td>
<td>–7.10</td>
<td>.000</td>
</tr>
<tr>
<td>(\sigma^2) (residual variance)</td>
<td>1.18</td>
<td></td>
</tr>
</tbody>
</table>

HLM model 4: intercept as outcome model

<table>
<thead>
<tr>
<th>Fixed effects</th>
<th>Estimate&lt;sup&gt;*&lt;/sup&gt;</th>
<th>SE</th>
<th>t</th>
<th>df</th>
<th>Pr &gt; t</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\gamma_0) (slope)</td>
<td>2.34</td>
<td>0.23</td>
<td>10.03</td>
<td>497</td>
<td>.000</td>
</tr>
<tr>
<td>(\gamma_1) (difference between urban and rural intercept)</td>
<td>–3.26</td>
<td>0.51</td>
<td>–6.36</td>
<td>3</td>
<td>.000</td>
</tr>
<tr>
<td>(\gamma_0) (rural intercept)</td>
<td>15.25</td>
<td>0.42</td>
<td>36.67</td>
<td>3</td>
<td>.000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Random effects</th>
<th>Estimate&lt;sup&gt;*&lt;/sup&gt;</th>
<th>Pr(H&lt;sub&gt;0&lt;/sub&gt;: (\tau = 0))</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\tau_0) (variability in clinic intercepts after adjusting for urban or rural location)</td>
<td>0.55</td>
<td>.000</td>
</tr>
<tr>
<td>(\sigma^2) (residual variance)</td>
<td>1.28</td>
<td>Table 2 continues</td>
</tr>
</tbody>
</table>
The results from applying this model to the alcohol data set are shown in Table 2 (see REG model 1). These results indicate that, on average, 1 additional hour of physician advice is associated with an increase of 1.31 alcohol-free weeks; however, this increase does not reach statistical significance at the 5% level, so these results would lead us to conclude that physician advice does not impact patient alcohol consumption. The residual variance in number of alcohol-free weeks after adjusting for hours of advice ($\sigma^2$) is about 2.1. Figure 1b shows the predicted regression line for the entire data set based on this model.

Robust regression methods, which involve only a slight modification of traditional linear regression analysis, address some of the problems described above and can be used as sensitivity analyses when the emphasis is primarily on fixed effects.10

Careful exploration of the data reveals that the mean number of alcohol-free weeks without any physician advice—intercept ($b_0$)—may be different in different clinics (Figure 2a). This baseline heterogeneity across clinics is illustrated in the figure, which shows the traditional model 1 fit individually for 2 clinics. Further exploration of the data reveals that the effect of physician advice—slope ($b_1$)—may also vary across clinics (Figure 2b), suggesting that physicians’ advice (per unit of time spent) is more effective at some clinics than at others. This figure illustrates the model fit of the traditional model 1 in a third clinic, which suggests that besides differences in mean number of alcohol-free weeks without any physician advice (variation in intercepts), there are also differences in the effect of hours of physician advice (variation in slopes) on patient number of alcohol-free weeks across clinics.

**Multilevel Models**

Multilevel models provide a way to account for variation in intercepts and slopes across clinics (level-2 units) without having to apply the traditional model 1 separately for each clinic. The random-intercept model, which allows for variation in intercepts across clinics, is a simple model in the series of HLMs, whereas a more advanced model, the random-coefficients model, accounts for variation in both intercepts and slopes across clinics. These models are described below and in the online Supplemental Appendix. Researchers can use a variety of statistical programs to analyze multilevel data:

- HLM (Raudenbush, Bryk, Cheong, and Congdon; available at http://www.ssicentral.com/hlm/hlm.htm)

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### Table 2 continued

**HLM model 5: intercept and slope as outcomes model**

<table>
<thead>
<tr>
<th>Fixed effects</th>
<th>Estimate*</th>
<th>SE</th>
<th>t</th>
<th>df</th>
<th>Pr &gt; t</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\gamma_{11}$ (difference in slope between urban and rural areas)</td>
<td>3.97</td>
<td>0.50</td>
<td>7.94</td>
<td>3</td>
<td>.000</td>
</tr>
<tr>
<td>$\gamma_{10}$ (average slope in rural areas)</td>
<td>0.67</td>
<td>0.44</td>
<td>1.54</td>
<td>3</td>
<td>.220</td>
</tr>
<tr>
<td>$\gamma_{01}$ (difference in intercepts between urban and rural areas)</td>
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<td>0.83</td>
<td>–6.67</td>
<td>3</td>
<td>.000</td>
</tr>
<tr>
<td>$\gamma_{00}$ (average intercept in rural areas)</td>
<td>16.15</td>
<td>0.60</td>
<td>26.77</td>
<td>3</td>
<td>.000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Random effects</th>
<th>Estimate*</th>
<th>Pr($H_0: \tau = 0$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tau_{00}$ (variability in intercepts after adjusting for urbanicity)</td>
<td>1.51</td>
<td>.000</td>
</tr>
<tr>
<td>$\tau_{10}$ (variability in slopes after adjusting for urbanicity)</td>
<td>0.28</td>
<td>.092</td>
</tr>
<tr>
<td>$\tau_{01}$ (covariance between intercept and slope)</td>
<td>–0.44</td>
<td></td>
</tr>
<tr>
<td>$\sigma^2$ (residual variance)</td>
<td>1.39</td>
<td></td>
</tr>
</tbody>
</table>

**REG model 2: traditional regression model 2**

<table>
<thead>
<tr>
<th>Fixed effects</th>
<th>Estimate*</th>
<th>SE</th>
<th>t</th>
<th>Pr &gt; t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope $\gamma_{11}$ (urban – rural)</td>
<td>1.48</td>
<td>1.13</td>
<td>1.30</td>
<td>.226</td>
</tr>
<tr>
<td>$\gamma_{10}$ (rural)</td>
<td>0.83</td>
<td>0.49</td>
<td>1.71</td>
<td>.163</td>
</tr>
<tr>
<td>Intercept $\gamma_{01}$ (urban – rural)</td>
<td>–4.04</td>
<td>1.01</td>
<td>–4.01</td>
<td>.016</td>
</tr>
<tr>
<td>$\gamma_{00}$ (rural)</td>
<td>16.05</td>
<td>0.67</td>
<td>23.94</td>
<td>.000</td>
</tr>
</tbody>
</table>

---

* Estimated number of alcohol-free weeks during the past year.
† Residual variance = 2.0813.
MULTILEVEL MODELING

• WinBUGS (MRC Biostatistics Unit, Cambridge, United Kingdom; available at http://www.mrc-bsu.cam.ac.uk/bugs/welcome.shtml)

HLM Model 2: Random-Intercept Model
The random-intercept model accounts for the variation across clinics in the mean number of alcohol-free weeks without any physician advice (online Supplemental Appendix, see HLM model 2); however, the effect of physician advice (per unit of time spent) is still constrained to be the same for all clinics (ie, the slope is fixed). This model is equivalent to a 1-way analysis of covariance (ANCOVA) with random effects (intercepts).

Statistical packages for multilevel modeling allow for estimation of all parameters in this model, including the random effects, and enable us to test whether there is significant variation among clinics, after adjusting for patient- and clinic-level covariates. This test helps us to determine whether it is necessary to retain a clinic-level random effect. The results from applying the random-intercept model to the alcohol data set are shown in Table 2 (see HLM model 2). The ICC (ratio of the between to the total variance) is about 68%, indicating that patients within clinics are very similar to each other compared with patients in different clinics. Consequently, after accounting for differences among clinics, the estimate for the residual variance ($\sigma^2$) is reduced to 1.65. Moreover, the estimate of the effect of physician advice, per unit of time spent, on patient alcohol-free weeks—slope ($\gamma_0$)—is now 2.38 alcohol-free weeks per unit time spent and is statistically significant at the 5% level. From these results, we would conclude that time spent by physicians advising patients on alcohol consumption does have an effect on their alcohol consumption (it is also possible to gain in precision but lose in significance). In this case, wherein between-clinic differences are large, the gain in efficiency with the HLM estimator provides 2 advantages over the traditional models: (1) it can affect policy decisions by influencing the significance of the estimates, and (2) it reduces the instability in point estimates of parameters because of the tighter error variance.

HLM Model 3: Random-Coefficients Model
In the random-coefficients model, we allow both the intercept and the slope to be specified as random variables (Figure 2b showing individual regressions for each clinic), thus accounting for variability in both the mean number of alcohol-free weeks without any physician advice (intercepts) and the effects of physician advice (slopes) across clinics. As a result, if clinics were analyzed in separate linear regression models, estimates for intercepts and slopes could be quite different from one clinic to the next. These differences are ignored when data from different clinics are combined in a simple linear regression model or even in a random-intercepts model, and ignoring them can result in incorrect conclusions, such as erroneously concluding that physician advice does not affect patient alcohol consumption.

(Note: It is possible to estimate clinic differences using a combination of indicator variables and interaction effects in traditional linear regression, but this practice is not recommended because the assumption of independence is still violated, power is severely hampered, and too many terms may be required for the sample size.)

The online Supplemental Appendix (see HLM model 3) gives details of the random-coefficients model, and Table 2 (see HLM model 3) shows the results obtained when this model is applied to the alcohol data set. We can see that there is significant
variability in the mean number of alcohol-free weeks without any physician advice across clinics, as well as variability in the effect of physician advice on alcohol consumption across clinics (reject the null of $H_0: \tau = 0$). The average slope in the entire study population is estimated to be 2.96 and is statistically significant at the 5% level. Also, the covariance parameter estimate, which describes the relationship between the intercepts and slopes, is negative ($\tau_{ij} = -7.10$). It is therefore possible that physician advice in clinics with a higher baseline number of alcohol-free weeks may have less impact than in clinics with a lower one (a possibility that should be tested more rigorously to determine whether it is a real clinical effect).

**More-Complex Models**

In the previous HLMs, we have allowed the intercept and the slopes to be random (vary across clinics) in order to account for the variability in mean number of alcohol-free weeks without physician advice and the variability in the effects of physician advice across clinics. The next logical step is to try to explain these differences among clinics using characteristics of the level-2 units (clinics).

**HLM Model 4: Intercept as Outcome Model**

With the intercept as outcome model, we want to see if variability in the mean number of alcohol-free weeks without any physician advice across clinics (intercepts) can be explained by clinic-level characteristics such as urban or rural location of the clinic (online Supplemental Appendix, see HLM model 4). Like HLM model 2, this model assumes that the effect of physician advice on alcohol consumption (slope) is the same across clinics.

The results for the intercept as outcome model are given in Table 2 (see HLM model 4). The results show that the mean number of alcohol-free weeks without any physician advice (ie, $x_{ij} = 0$) is about 15.25 for patients in rural clinics, whereas it is about 3.26 weeks lower for patients in urban clinics. This difference is statistically significant at the 5% level. Moreover, urbani- city of the clinic explains about 84% of the variance in the intercept. This observation suggests that a substantial amount of the variability in baseline number of alcohol-free weeks across clinics can be accounted for by urban or rural location; nevertheless, the variability in the intercepts is still significant even after adjusting for clinic location.

**HLM Model 5: Intercept and Slope as Outcomes Model**

In the intercept and slope as outcomes model, we try to explain both the variability in the baseline number of alcohol-free weeks (intercepts) across clinics and the variability in the effect of physician advice on alcohol consumption across clinics (slope) by clinic-level characteristics such as urban vs rural location of the clinic (online Supplemental Appendix, see HLM model 5).

Study results obtained when the intercept and slope as outcomes model is applied to the alcohol data set are given in Table 2 (see HLM model 5). The results show that after adjusting for urbanicity of clinics, the remaining variability in slopes is not statistically significant ($P = .092$) at the 5% level (although it is significant at the 10% level). The researcher may decide to retain the random slope or may choose to specify the slope as nonrandomly varying. The results also show that the effect of physician advice on alcohol consumption is nonsignificant in rural clinics (0.67 alcohol-free weeks per hour of physician advice, $P = .220$), but there is a significant difference in this effect between urban and rural clinics (difference of 3.97 alcohol-free weeks per hour of physician advice, $P = .000$). For urban clinics, an additional hour of physician advice is associated with an increase of 4.64 (ie, 3.97 + 0.67) additional alcohol-free weeks on average.

**REG Model 2: Traditional Regression Model 2**

In a traditional patient-level model, a main effect for physician advice, a main effect for urbanicity, plus an interaction term (physician advice $\times$ urbanicity) would be used to study how urban vs rural location moderates the effect of physician advice on alcohol-free weeks (online Supplemental Appendix, see REG model 2). This approach allows the intercept and the slope to vary for urban and rural locations but is problematic if there is significant variability among intercepts and slopes of clinics within location type. The results for the traditional regression model 2 are shown in Table 2 (see REG model 2). Unlike the intercept and slope as outcomes model above (HLM model 5), this model shows that the difference in the effect of physician advice on alcohol consumption between the urban and rural clinics is nonsignificant. Had we used this model, we would have concluded that physician advice was ineffective for rural clinics and that the effect of physician advice in urban clinics did not differ from that in rural clinics.

**How Important Are Modeling Decisions in PBRN Studies?**

Can different analytic approaches affect an investigator’s conclusions about the outcome? The results in Table 2 show that decisions about the potential effectiveness of physician time spent advising patients on alcohol consumption may vary with the choice of analytic approach. Had the researchers ignored the hierarchi- cal structure of the data and used traditional analytic approaches, they would have erroneously concluded
that physician advice had little or no influence on patient alcohol consumption behavior. On the other hand, all the HLMs that assess the relationship between physician time advising patients on alcohol consumption and patient behavior lead to the conclusion that physician advice is effective, at least in some settings. An important limitation of the hypothetical study should be mentioned at this point. Because variability among clinic intercepts and slopes is estimated using clinic-level information, ideally, the number of level-2 units (clinics) should be much greater than 5. Several of the references cited below include discussions about how many level-2 units should be sampled.6,7

APPLICATIONS TO OTHER FORMS OF DATA AND INTERVENTIONS

Randomized Controlled Trials

The variety of HLMs described above can be readily extended to study different types of interventions and data that have some sort of group structure, such as clustering of patients within clinics. In intervention studies that are carried out in PBRNs, it is often necessary to randomize at the clinic level to avoid contamination and minimize difficulties in implementing interventions. This setup naturally leads to the use of multilevel modeling. For example, suppose we want to test an intervention to assist patients in their daily management of type 2 diabetes. The intervention might involve patient education and support from their primary care clinicians and be implemented at the practice level in 20 practices, with 10 randomized to the intervention and 10 to provision of usual care. We wish to control for patient characteristics, so patient-level covariates will be included in the level-1 model. We would allow the intercept and slope to vary randomly across practices and then try to explain this variability using the intervention variable as a level-2 characteristic (as in HLM model 5, the intercept and slope as outcomes model).

Longitudinal Models

Longitudinal models, in which individuals are observed at multiple instances over time, are actually another kind of hierarchical structure, in which level-1 represents the individual’s observations over time, and the level-2 units are the patients themselves. These models are discussed in detail elsewhere.6,7

Dichotomous Dependent Variables

Other forms of outcome data can be analyzed using hierarchical generalized linear models (HGLMs), also called generalized linear mixed models (online Supplemental Appendix, see HGLM model). For example, many health outcomes are dichotomous or binary rather than continuous (eg, a patient was tested for a particular condition, a patient achieved a target hemoglobin A1c level). Suppose in the example above, the intervention for diabetes included a physician education component designed to encourage primary care physicians to screen for hyperlipidemia among diabetic patients. The patient-level outcome is whether the patient was screened (yes or no) within a designated time period after the intervention. We want to control for patient characteristics and test whether the intervention is effective at encouraging physicians to screen their diabetic patients. In the traditional approach to this analysis, we might use a logistic regression model; however, the assumption of independence of observations is violated because of the clustering of patients within clinics. One alternative approach (there are other possible approaches) adapts the hierarchical linear model by using a link function at level 1 that is appropriate to the distribution of the outcome variable.5

Higher-Level Data Structure

Finally, it is straightforward to extend a 2-level hierarchy to a hierarchy of 3 or more levels. Interested readers are referred to Bryk and Raudenbush1 for a detailed description of these models. A number of useful statistical references are given below.8-12

OTHER ISSUES

Measurement and Variable Specification in Multilevel Models

Characteristics of patients, physicians, and practices constitute a set of interrelated factors that can be conceptualized and measured at different levels of a hierarchical system. In multilevel modeling, researchers must pay careful attention to the specification of variables, with measurement at the appropriate level. Some measurement issues that are specific to multilevel models differ from those of traditional psychometric approaches, focusing instead on level of measurement, ways of operationalizing higher-level constructs, and empirical support for types of composition processes for aggregating lower-level data to form macrolevel variables. Variables that provide information about higher-level units (eg, clinicians or settings) can be measured directly or created from measures aggregated from lower-level units (eg, patients). Researchers must exercise caution, however, in avoiding aggregation bias when creating variables and in interpreting results because meaning and functional relationships in multilevel models may be different at lower and higher levels of the hierarchy.1 In the example on counseling about alcohol consumption, the effect of average (aggregated) time spent on such advice in a clinic may reflect a clinic's
Table 3. Examples of Sample Sizes for Group-Randomized Designs

<table>
<thead>
<tr>
<th>Original Sample Size*</th>
<th>No. of Clinics</th>
<th>No. of Patients per Clinic (m)</th>
<th>ICC</th>
<th>VIF</th>
<th>Adjusted Sample Size*</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>25</td>
<td>4</td>
<td>.00</td>
<td>1.0</td>
<td>100</td>
</tr>
<tr>
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<td>29</td>
<td>4</td>
<td>.05</td>
<td>1.15</td>
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<td>.10</td>
<td>3.4</td>
<td>340</td>
</tr>
</tbody>
</table>

m = designator for number of patients per cluster to be used in calculations; ICC = intraclass correlation coefficient; VIF = variance inflation factor.

*Number of patients per treatment group.

CONCLUSIONS AND RECOMMENDATIONS

PBRN research generally involves sampling patients from multiple practice sites and often involves group randomization approaches to intervention studies. Data resulting from such approaches are inherently hierarchical. Recognizing the need for adjustments to study design and data analysis in the presence of clustering can allow PBRN investigators to arrive at more accurate conclusions and to more appropriately estimate sample size requirements. Methodologic advances also offer rich opportunities to explore contextual effects by using models that incorporate characteristics of clinicians and clinics as well as those of patients.

To read or post commentaries in response to this article, see it online at http://www.annfammed.org/cgi/content/full/3/Suppl_1/S52.

Key words: Practice-based research network; cluster analysis; clustered data, multilevel models; data analysis; models, statistical; data interpretation, statistical

Power

In the data analysis on alcohol consumption, the ICC is quite high, but even a relatively small ICC can have adverse effects on power, requiring a larger sample size. Using the Donner et al formulae for the variance inflation factor (VIF), which is also referred to as the design effect, we can determine adjusted sample size requirements in the presence of clustering. If an unclustered design for a randomized controlled trial requires patients per group to detect the desired effect size with adequate power (eg, 80% power) and \( \alpha = .05 \), then the VIF allows us to adjust the sample size for a positive ICC. If we sample patients per cluster clinic, then we must inflate the sample size by a factor of \( 1 + (m - 1) ICC \). Table 3 gives a range of sample size corrections for cluster designs with a starting sample size of 100 patients per treatment condition and varying numbers of patients per cluster (clinic) and ICC. It is readily apparent from this table that sample size requirements for clustered designs can be drastically affected by large cluster sizes and increasing ICCs.

References


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