

Public-Private Partnerships for Patient Registries

Draft White Paper for Third Edition of “Registries for Evaluating Patient Outcomes: A User’s Guide”

Introduction

As both government and private groups have shown increased interest in patient registries, public-private partnerships (PPPs) have become more common as a means to develop and support patient registries and data linkage projects. These types of partnerships may become more common, as recent legislative actions have suggested PPPs as a potential approach to registry development.¹ More information is needed on what types of public-private partnerships are possible, what issues should be considered when using such a partnership to develop or support a registry, and what characteristics and practices are likely to enhance the success of such efforts. This paper defines PPPs in the context of patient registries, provides examples of existing PPPs, discusses considerations for setting up and operating PPPs, and reviews key factors for successful partnerships. While the discussion in this paper primarily focuses on PPPs within the United States, some considerations for international partnerships are also reviewed.

Definition of a Public-Private Partnership

“Public-private partnership” is a broad term that refers to any partnership in which at least one entity is a public agency (e.g., a government entity) and at least one other entity is a private organization. The scope can range from partnerships at the local level, including local and regional health agencies, to national and international health agencies and other private institutions or organizations (e.g., professional associations, patient advocacy groups). A partnership implies some joint collaboration to achieve a common scientific goal. Partners may contribute intellectual capital, funding, data, or other services.

Public-Private Partnership Models

Public-private partnerships may take many forms. Some possible models include partnerships among Federal agencies to examine safety and effectiveness (e.g., INTERMACS); partnerships among health agencies from several countries on an international level to describe the clinical course of a disease and

understand whether there are any effective treatments (e.g., Avian Flu Registry); partnerships with state agencies for quality improvement (e.g., Get With The Guidelines); and partnerships for evidence development for coverage decisions (e.g., Centers for Medicare and Medicaid Services). These models are described below, as case studies.

INTERMACS

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) is the United States national registry for patients who have received durable, FDA-approved mechanical circulatory support device (MCS) therapy to treat advanced heart failure. This registry was devised as a joint effort of the National Heart, Lung and Blood Institute (NHLBI), the Centers for Medicare and Medicaid Services (CMS), the Food and Drug Administration (FDA), clinicians, scientists and industry representatives. The goals of the registry are to:

- Facilitate the refinement of patient selection to maximize outcomes with current and new device options;
- Identify predictors of good outcomes as well as risk factors for adverse events after device implantation;
- Develop consensus “best practice” guidelines to improve clinical management by reducing short and long term complications of MCS therapy; and
- Utilize registry information to guide clinical application and evolution of next generation devices.

A major challenge to INTERMACS was to create a registry with sufficient data quality, regulatory rigor, and sophistication to be able to achieve these goals. INTERMACS used the quality of a high-level clinical trial as its standard, realizing that it could never totally meet these standards but could emulate them as closely as possible in a structured, protocol-driven manner. See Table 1 for a listing of the regulatory, data quality, and scientific components of a clinical trial and which of these components are contained in INTERMACS.

Table 1: Regulatory, Data Quality and Scientific Components of a Typical FDA Clinical Trial and INTERMACS

	Typical FDA Clinical Trial	INTERMACS
DSMB/OSMB	✓	✓
Informed consent	✓	✓
IRB approval	✓	✓
Data use agreement	✓	✓
Human subjects training	✓	✓

	Typical FDA Clinical Trial	INTERMACS
Information security	✓	✓
Active website	✓	✓
Protocol	✓	✓
CLIA certification	✓	✓
Adjudication	✓	✓
Local PI certification	✓	✓
Data freezes	✓	✓
Audits	✓	✓
Complete enrollment	✓	✓
Complete data	✓	✓
AE definitions	✓	✓
Inclusion/exclusion	✓	✓
Nurse monitors	✓	✓
Site training	✓	✓
Site reports (QA, etc.)		✓
Standardized datasets	?	✓
Medical device reports to FDA	✓	✓
Mandatory data entry	✓	✓
Planned analyses	✓	✓
DAAP: research requests	?	✓
Annual meetings	✓	✓
Committees	✓	✓

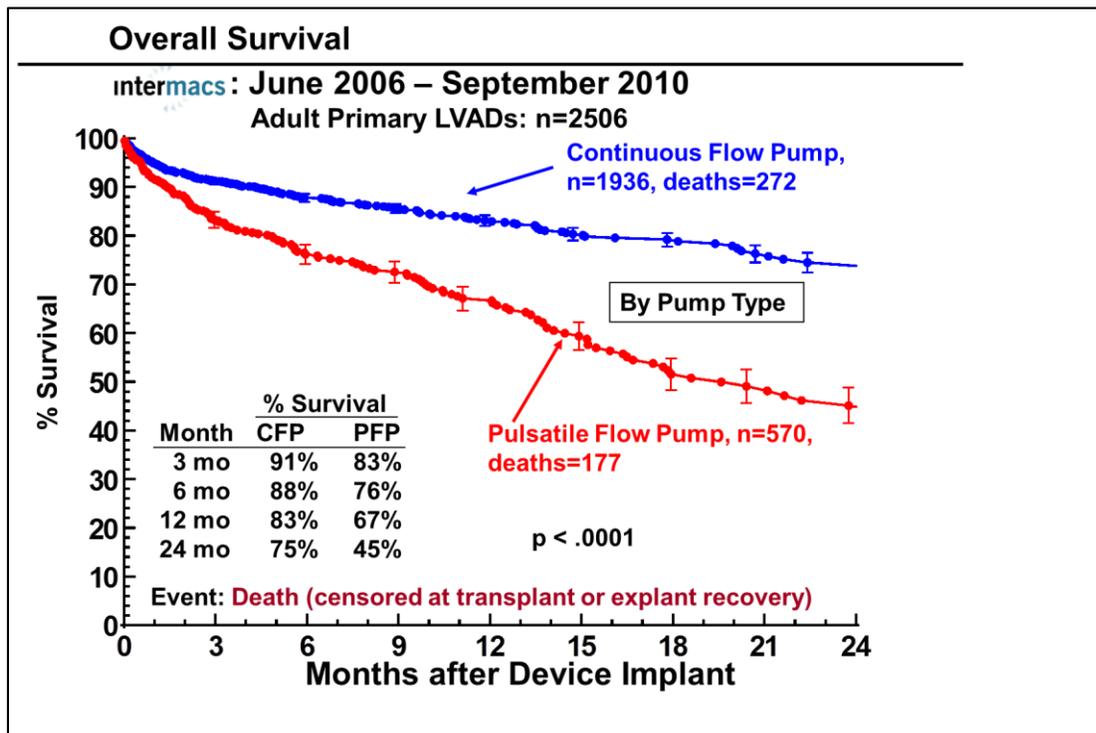
Another major challenge to INTERMACS is to maintain focus on its mission while many tangential efforts and registry “by-products” have appeared. For example, INTERMACS has offered a new regulatory pathway for industry as FDA approval is sought for new devices. It also has provided the control arm for one FDA pre-market approval trial and is in the process of providing control data for several ongoing and new trials. While these efforts were not part of the initial goals and contract deliverables of INTERMACS, they do, in general, fit the mission of moving the field forward.

In 2005, the original contract between NHLBI and the Division of Cardiothoracic Surgery at the University of Alabama at Birmingham (UAB) specified a target enrollment of 40 to 60 hospitals. As of July 2011, 120 hospitals have enrolled and have entered data on more than 5,000 patients.

The complexity of managing a patient with a mechanical circulatory assist device requires a similarly complex registry. Implantation of a left ventricular device, a right ventricular device, and/or a total heart replacement device must be captured along with subsequent device explants, multiple adverse events, functional capacity, and quality of life. The INTERMACS clinical research forms are numerous and detailed, with more than 1,500 data elements.

A unique feature of INTERMACS is that it is assessing a rapidly changing clinical and technological field. INTERMACS must be poised to quickly assess newly approved devices and to quantify the evolution in patient selection. Figure 1 shows survival based on two types of devices. These devices correspond to eras with the intracorporeal continuous flow pump being the most recently approved MCS/D. The improvement in survival is dramatic, and INTERMACS has been the best way to quantify this improvement.

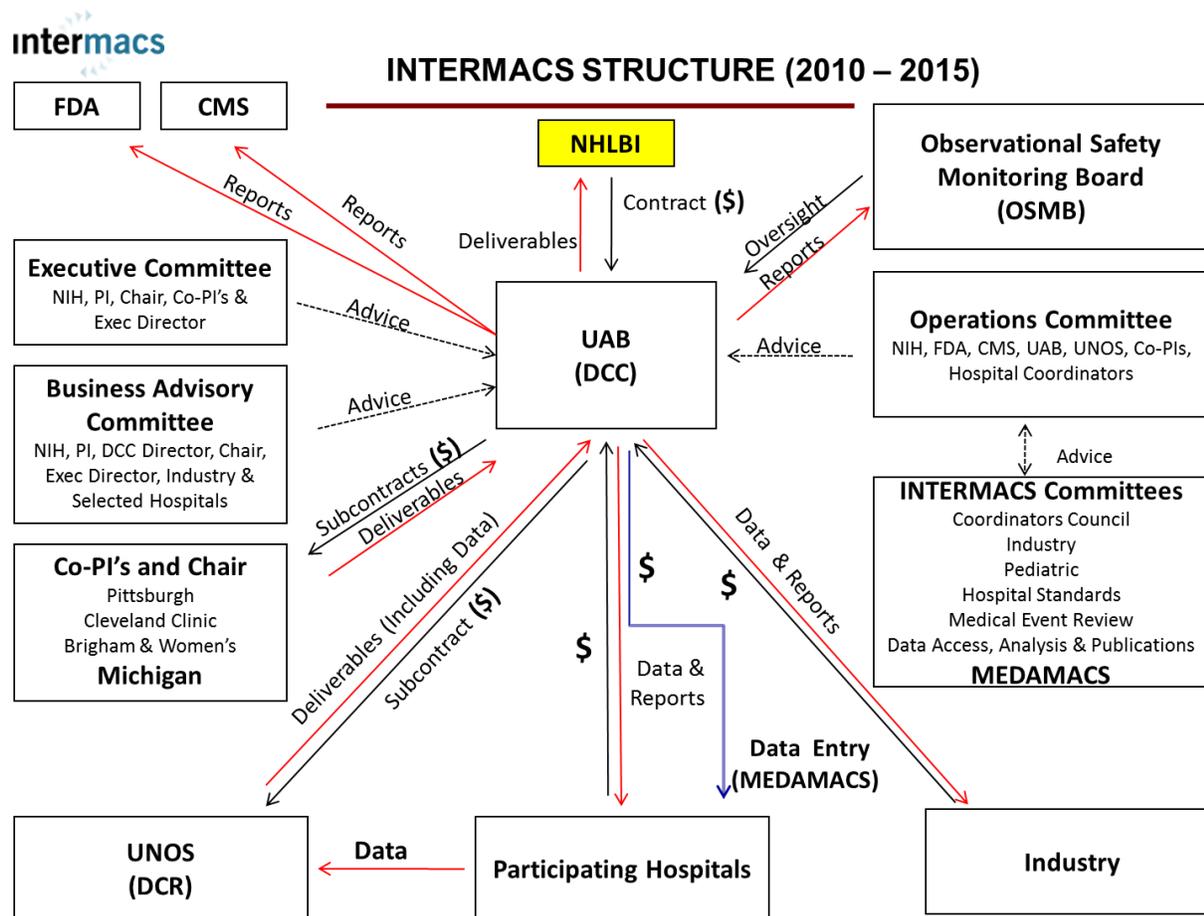
Figure 1: Overall Survival of Adult INTERMACS Subjects Receiving Primary Left Ventricular Assist Devices (LVADs), by Pump Type



Initially, INTERMACS was the result of an NHLBI initiative in collaboration with FDA and CMS. Other stakeholders quickly joined in the planning stage, and they have continued to be INTERMACS partners. These multiple partners each have their own agendas and their own reasons for participating in INTERMACS. While their goals do not always align, there is considerable overlap, and INTERMACS has been able to fulfill most needs for each partner. At the intersection of these agendas are the common goals of assessing current devices and contributing to the development of new devices by analyzing registry data. The ultimate goal for all of the partners is to improve patient outcomes.

Figure 2 is a schematic representative of the partners involved in INTERMACS. The relationships are necessarily complex and must be managed by clear expectations, deliverables, standard operating procedures, and lines of authority.

Figure 2: Structure of INTERMACS Partners



Stakeholders

NHLBI. As the sponsoring agency, NHLBI is both the primary partner and primary regulator of the registry. In addition to its oversight role, NHLBI has been involved in many of the day-to-day activities of INTERMACS, including the important role of ensuring scientific and regulatory integrity and patient protection.

FDA. Through their regulatory role in approving and monitoring new devices, the FDA functions as the “gatekeeper” for devices. INTERMACS benefited from early interactions with FDA in developing the specifications of data elements and definitions of adverse events. As INTERMACS evolved, it worked

with two separate components of FDA. The pre-market personnel at the Center for Device and Radiological Health (CDRH) helped create a registry that would build on the previous pre-market approval studies of MCSD. INTERMACS also worked with the post-market approval personnel of CDRH to explore ways to facilitate the analyses of approved devices. The partnership with FDA has evolved as INTERMACS has become a major post-market study vehicle for approved MCSDs, as evidenced by the collaboration with Thoratec and FDA to perform the post-market studies for HeartMate II, the first FDA-approved adult non-pulsatile pump.

CMS. When INTERMACS began, CMS was reimbursing hospitals for FDA-approved MCSDs that were implanted as destination therapy (DT) at approved centers. One of the requirements of the reimbursement was that data on implanted patients be entered into a national database. By the third year of INTERMACS, CMS changed the requirement to explicitly specify INTERMACS as the data repository and stated that a certified DT center must be in good standing with INTERMACS. This partnership with CMS has been critical to the development of a comprehensive database that captures the vast majority of approved durable devices implanted as DT or as bridge-to-transplant therapy.

Joint Commission. The Joint Commission is responsible for certifying hospitals as DT centers. INTERMACS collaborates with CMS, The Joint Commission, and hospitals to assist in the quantitative summaries necessary for certification.

Industry. Essentially every company that manufactures approved MCSDs or is in the process of gaining approval for an MCSD has been involved with INTERMACS. Industry was “at the table” during the meetings to develop INTERMACS. Many companies saw great potential for using INTERMACS in both pre-market clinical trials and post-market studies. The FDA has encouraged companies to work with INTERMACS. Some of these activities fall outside of the strict deliverables of INTERMACS but do fall within its goals.

Hospital Collaborators (Physicians, Surgeons, Coordinators, Administrators, and Quality Assurance Officers). The scientific and clinical energy of INTERMACS comes from physicians who care for heart failure patients and surgeons who implant the devices. The hospitals, via their coordinators, provide the data that populates the registry. INTERMACS serves as an important resource for the hospitals in activities related to mechanical circulatory support. For example, hospitals can submit requests for scientific studies, obtain their own electronic data from INTERMACS, and participate in an INTERMACS forum (the Coordinators Council) for coordinator feedback and discussion of relevant mechanical circulatory support topics. INTERMACS provides quarterly reports to participating hospitals

that summarize and analyze their patients and provide benchmarking against registry-wide data. Patient-level reports that provide a chronological history of the patient's MCSD-related events are also available. These clinical summaries are an important tool in the data quality process.

Other Entities. In addition to the formal partners of INTERMACS, a number of other entities have requested collaboration. These include regulatory bodies of foreign governments, scientific societies, foreign hospitals, insurance companies, investment firms, and the media. Each request for collaboration is handled on an individual basis and considered within the framework of the goals and regulatory structure of INTERMACS.

Avian Flu Registry

Highly pathogenic infectious diseases continue to emerge, with substantial public health and financial tolls. Three features of newly emerged communicable diseases are immediately salient to registry development and use:

1. Communicable diseases do not respect international borders.
2. Communicable diseases, by their very nature, usually constitute a significant public health threat.
3. Emerging communicable diseases usually enjoy a high media profile and are the subject of significant interest to the public.

Consider the recent H1N1 influenza pandemic and SARS as examples. While many newly emerged infections first manifest themselves in exotic or tropical locations, this is not an invariable rule, as shown by the emergence of legionellosis in Philadelphia.

The facility with which communicable diseases are able to cross international borders means they typically receive global attention, especially in our current era of mass international travel and globalization of trade. The fact that newly emerged infections usually represent a threat to public health means that governments and their agencies usually become involved in their investigation and management, typically at an early stage. Public concern, often fuelled by the media, may add to pressures upon public health authorities to react and to be seen as reacting to newly emerged threats. As a consequence, entities wishing to investigate newly emerged infections will generally need to engage with public health authorities, typically at a national government level.

A prime example of such a collaboration is the Avian Flu Registry, set up to investigate infection with influenza A/H5N1, a disease with almost 90% mortality if untreated.^{2,3} The registry, which began in

2007, is a multi-country, observational study of the diagnosis, treatment, and outcomes of human cases of the A/H5N1 virus. Data are collected from health care professionals, and information abstracted from detailed, published case studies is also included (see the “Using a Registry To Track Emerging Infectious Diseases” case example¹ for more information). The registry has built a multinational, multicenter collaboration that houses the world’s largest collection of human avian influenza cases and has made important contributions to understanding the treatment effectiveness for this highly lethal disease.^{4,5} Its success has been built upon recognition of the unique nature of emerging infections, recognition of the differing needs of developing countries and collaborators, and adoption of a flexible and pragmatic approach. Its success is also attributable at least in part to the establishment of successful collaborations with national public health agencies in a number of countries.

However, the establishment of such collaborations is not always a straightforward matter, especially when initiated by the private sector. Newly emerged infections usually become politicized quite soon after their initial appearance. The classic example of this phenomenon is HIV, but SARS and pandemic influenza were also politicized rapidly after emergence. This politicization is seen in both economically developed democracies and developing countries. Further and deeper politicization may ensue when the newly emerged infection is viewed by afflicted countries as stigmatizing them in some way or is seen as a matter of national security; the response of some governments to avian flu exemplifies these types of responses. Similar reactions were seen in Indonesia with H5N1 and in China with the early stages of SARS. Developing countries may also be sensitive to the fact that their health care systems do not offer the same level of care as is available in developed countries. These countries may also lack developed disease surveillance systems and may feel uncomfortable at this lack being exposed.

Considering these sensitivities, the establishment of registries to study newly emerged infections may require a different approach to that typically adopted in other disease areas. An understanding of local sensitivities and a willingness to attend to local needs and to answer local questions will be helpful. An avoidance of a ‘one size fits all’ approach should also prove helpful, with flexibility to react to different countries in different ways being important. A useful guiding principle in the establishment of such multinational collaborations is to place the needs of the collaborator first, rather than the needs of the entity establishing the registry. While national public health authorities may well understand the altruistic nature of much global public health research, their constituencies remain local, and they are answerable to

¹ Case Examples referenced in this document can be found in the second edition of “Registries for Evaluating Patient Outcomes: A User’s Guide,” available at: <http://www.effectivehealthcare.ahrq.gov/ehc/products/74/531/Registries%202nd%20ed%20final%20to%20Eisenberg%209-15-10.pdf>.

their local political masters and public. Working in this type of environment adds an additional layer of complexity, but this has to be successfully navigated if success is desired.

The Avian Flu Registry provides a good example of these political issues and how they might be surmounted. A complaint frequently heard when approaching ministries of health for collaboration was that such previous efforts had yielded little or no benefit to the participating country, with little or no feedback once collaboration had been agreed and data entry completed. The Avian Flu Registry, from inception, took pains to ensure prompt feedback to collaborators of data analyses and registry findings and to respond to requests from collaborators for further analyses in a positive and timely manner.

The funding for the Avian Flu Registry came from a pharmaceutical company that had a marketed product for treatment of seasonal influenza. Since hardly any information was available about avian influenza, the registry sponsor wanted to learn more about the illness with an eye toward understanding if their product would be effective for this more lethal flu strain. While some may see primary funding from industry as a disadvantage, the apolitical nature of this funding may actually have been advantageous. The relationship between the funder and the scientists charged with building the registry was clearly established at the earliest stage of planning and documented in a clearly worded binding contract. It was in the interests of the industry sponsor to step back from operational issues, allowing the investigators to build an international collaboration with the sole purpose of understanding the disease, with the expectation this would be done as efficiently as possible and with findings to be shared with all participants.

In addition, the registry was created in its earliest stages to conform to principles of good practice for registry science, including formal ethical review, a Steering Committee, and various other governance structures that proved useful throughout the program. A complexity of the registry was its broad global reach, which included collaborators from 13 different countries. The nature of regulations varied by country and by collaborator, but was in all instances compatible with the founding documents of the registry, as enshrined in the agreement between the industry funder and the investigators, and as presented to an independent ethics review board. A formal Memorandum of Understanding outlined all the key principles for data sharing, protection of privacy, ethical review, etc. Original documents guaranteed protection of the identity of individual reporting countries, a restriction that was later lifted by mutual agreement once it became apparent that country-specific factors like viral clade and barriers to access to care tempered treatment effectiveness. The Data Access and Publications Committee also proved to be useful in terms of providing a formal mechanism for recording, reviewing, and prioritizing research questions that were posed to the registry.

Get With The Guidelines®

Get With The Guidelines® is a hospital-based quality improvement program operated by the American Heart Association. The program aims to improve in-hospital care for patients by providing tools to support adherence to clinical practice guidelines. Hospitals pay a fee to participate in the program, which involves collecting and submitting data on patients. The program uses the data to generate benchmarking reports and to provide real-time feedback on adherence to the clinical practice guidelines. The program has been successful at demonstrating sustained quality improvement at participating hospitals.⁶

State-level departments of health also have an interest in improving quality at hospitals within their state. However, the development of a comprehensive quality improvement program is often not feasible given resource and staff constraints. In several cases, state departments of health partnered with the American Heart Association to sponsor hospitals in the Get With The Guidelines program. The state agencies paid the program fee for participating hospitals and, in return, received reports on hospital performance on a quarterly basis. Hospitals agreed to share their performance data, which the program would normally keep confidential, in return for receiving free access to the Get With The Guidelines program.

Centers for Medicare and Medicaid Services (CMS) Coverage with Evidence Development

In 2006, CMS issued a guidance titled “National Coverage Determinations with Data Collection as a Condition of Coverage: Coverage with Evidence Development”⁷ that presented a new option for CMS when determining whether a drug or device would be covered under Medicare or Medicaid. In addition to the existing possible decisions of “no change in current coverage,” “non-coverage,” and “coverage without special conditions,” CMS could now grant “coverage with special conditions,” in which:

“The medical evidence is adequate to conclude that the item or service is reasonable and necessary [...] only under one or more of the following circumstances:

- a. The item or service is covered only for patients with specific clinical or demographic characteristics.
- b. The item or service is covered only when provided by physicians and/or facilities that meet specific criteria.
- c. The item or service is covered only when specific data are submitted in addition to claims data to demonstrate that the item or service was provided as specified in the [national coverage determination].”⁸

Registries are particularly suited to this type of prospective data collection. This new Coverage with Evidence Development (CED) requirement spurred the creation of multi-stakeholder registries to facilitate data collection for drugs and devices receiving CMS coverage conditional on evidence development. Aside from CMS, which provides the incentive for the data collection, major partners often include professional associations (who contribute scientific guidance) and industry (who contribute funding). Registries that have been created or adapted to meet CED requirements include the National Oncologic PET Registry (NOPR) for the use of positron emission tomography to treat certain types of cancers⁹ and the ICD Registry for the use of implantable cardioverter defibrillators.¹⁰

Considerations for Setting up a Public-Private Partnership

Governance

A public-private registry is, by definition, a collection of stakeholders who have different purposes and agendas that hopefully overlap at the intersection of clinical science and improved patient care. In order to keep the registry focused, the registry needs a central authority. Often, this central authority is the Principal Investigator (PI), who oversees the registry and is responsible for developing consensus among stakeholders. The PI is also responsible for ensuring that the registry and the analyses of the registry data remain scientifically relevant and unbiased. The PI's scientific and operational oversight can be augmented by an Advisory Committee, which can include co-PIs and representatives from various partners in the registry (e.g., funding sources, reporting entities, or subcontractors that handle operational aspects of the registry).

Operational Decisions

Many registries are complex in nature with operational components including regulatory, financial, informed consent, data entry software, progress reports, periodic meetings, and scientific analyses. These registries are essentially small businesses that require intense day-to-day operations that should fall within a well structured effort. The structure of the registry efforts should be clear, with well-defined lines of authority and responsibility. The structure should also have the flexibility to adapt to changing science and the changing national landscape of regulatory requirements, such as the evolving nature of the Health Insurance Portability and Accountability Act (HIPAA) constraints. A representative Operations Committee that meets regularly to review the ongoing progress of the registry and to address issues as they arise may be desirable. This group can make decisions by consensus rather than a formal vote, and documentation (i.e., meeting minutes) should be created and distributed to memorialize decisions and actions taken.

Plans for Transparency and Communication

Transparency and ongoing communication are vital to the success of any complex registry, especially one that is a public-private partnership. An important vehicle for transparency can be a registry's public Web site, which can contain regulatory documents including the protocol and user's guide (see <http://www.intermacs.org>). The public face of the Web site for the Avian Flu Registry contains the registry prospectus and information about data security, along with an updated list of published scientific articles and presentations (see <http://www.avianfluregistry.org>), including many of the actual posters and slide sets for public viewing. Other options for engagement, transparency, and communication include periodic public stakeholder meetings, newsletters, and e-mail listservs.

Dispute Resolution

Disagreements, or even disputes, are inevitable when a group of diverse stakeholders collaborate on a single registry. As with any complex endeavor, the key to symbiotic working relationships lies in the initial formulation of the goals and expectations of the registry and of each collaborator. The responsibility of mediation and dispute resolution can be assigned to a leader within the registry, such as a Study Chair or PI, or can be handled by committee, as in the Avian Flu Registry.

Data Security

The data contained in any registry must be managed according to strict rules for data security, which can include secure password-protected access to data entry, secure transmission of data, background checks on personnel, personnel training on data security, virus scans of all computers, off-site backup of data, etc. Anyone creating a new registry is strongly advised to collaborate with information security experts, who can lead the registry through the data security requirements and can create protocols for security breaches.

Data Ownership, Data Access, and Publications

First and foremost, the data from a specific patient belongs to that patient. This belief is evident from the concept of informed consent and the ability of the patient to withdraw informed consent. Typically, a registry (i.e., the totality of the element based patient specific data) is owned by the registry sponsor. Therefore, data cannot be given to a third party without the express permission of the sponsor or according to internal registry policies that have been approved by the sponsor. However, generally once data have been provided to a registry, they cannot be withdrawn by collaborators unless a patient or his/her family specifically requests that it be withdrawn.

Data Access

A related question is who has access to the data. Data access should be guided by policies and procedures created by the Data Access and Publications Committee (DAPC). All data access should conform to HIPAA regulations, informed consent documents, and data use agreements (DUAs) between contributing sites and the registry. Many entities may request access to registry data, including some listed below.

- **Data provider or participating site.** Typically, the DUA between the site and the registry specifies that the site can request to receive all of its own data at any time, but may not request identified data from another site.
- **Registry sponsor.** The registry sponsor owns the data and therefore has complete access to all data. When the registry ends, the entire database is often transferred to the sponsor.
- **Regulatory agency (e.g., FDA, CMS).** A government regulatory agency may request registry data to fulfill safety reporting requirements or other obligations. In particular, if a sponsor has a marketed product that is used by any patients in the registry, that sponsor is subject to mandatory safety reporting requirements (see the Adverse Event Detection, Processing, and Reporting chapter²).
- **Industry.** Pharmaceutical companies or device manufacturers may request data of patients who receive their products, or may request registry data to use as controls for a clinical trial.
- **Investigators (within or outside the registry).** Investigators may request registry data for a particular research project; each request should be reviewed by the DAPC so that only the necessary data elements for the research project are shared.
- **Public.** Although rare, data requests from the media or the public are possible. Any information released to the public by the registry (via newsletters, public Web site, or other methods) should be reviewed prior to release, to ensure that data confidentiality is not compromised.
- **Standardized datasets.** Some registries produce de-identified, standardized datasets that are available to researchers on a periodic basis. These datasets contain no PHI, no product or treatment brand names, and no site identifiers, and they are often constructed to provide the information believed to be most helpful to researchers. The actual content of these standardized datasets and the policy for distribution should be governed by the DAPC, with approval by the registry sponsor.

² Chapters referenced in this document can be found in the second edition of “Registries for Evaluating Patient Outcomes: A User’s Guide,” available at: <http://www.effectivehealthcare.ahrq.gov/ehc/products/74/531/Registries%20nd%20ed%20final%20to%20Eisenberg%209-15-10.pdf>.

Process for Publications

Wherever possible, a registry should form a DAPC to prioritize research projects and handle data access requests. The committee should meet regularly to formally review, prioritize, and evaluate the requests based on the potential to impact clinical practice and the amount of data available to answer the research question. The DAPC can also work directly with an Advisory or Operations Committee to identify and facilitate internal research projects that directly address the stated research goals of the registry.

Process for Analyses

Depending on available resources, a registry can either conduct analyses to support publications in-house, contract an outside agency to conduct analyses, or leave this task to the data requestors themselves. If an outside agency or data requestor will be conducting analysis on registry data, a secure mechanism should be in place for sending the data to them. The DAPC should retain oversight of these activities, especially those that are intended to be used for manuscripts submitted to peer-reviewed publications.

Formal Documentation of Roles and Responsibilities

Whether a registry resembles a traditional public/private partnership (i.e., a group of stakeholders who come together to create and fund a registry) or a more unusual structure (i.e., a series of contracts and subcontracts that have precise deliverables), each entity is a collaborator in the sense that each partner provides something to the registry and receives something from the registry. For example, each hospital participating in INTERMACS provides the local effort for participation and data entry. The hospital also pays \$10,000 per year for participation. In return, the hospital receives many deliverables and benefits such as quarterly quality assurance reports, clinical summaries of each patient, electronic copies of their data, participation in research projects, and representation on the INTERMACS committees.

Because each entity may have numerous functions within a registry, it is important that roles and responsibilities be clearly defined and documented at the beginning of the registry. An Operations Committee can be charged with producing the roles and responsibilities document and updating it periodically as needed.

Funding

Registries can obtain their funding from a variety of sources. For example, INTERMACS was initially funded by a contract from NHLBI. During the second five year contract (December 2010 – November 2015), NHLBI asked UAB to develop a cost sharing plan that would allow NHLBI to significantly decrease their contribution while obtaining funding from private sources. The primary goal of this new arrangement was to obtain the necessary ongoing funding in order to achieve sustainability. This transition in funding is not unique to INTERMACS. Changes in funding are particularly common in

PPPs, where funding often comes from multiple sources. When funding sources change, it is often necessary to revisit the roles and responsibilities and data access policies to ensure that all stakeholders are represented appropriately.

Ethics

Conflicts of Interest

Because of the variety of stakeholders involved, a plan for identifying and managing actual and perceived conflicts of interest (COI) can be very useful, especially in high profile situations. In this context, COIs can be financial or intellectual. The plan should clearly spell out the timeline and process for obtaining completed COI and financial disclosure forms from participating members and for reviewing and managing any potential conflicts, particularly given any unique working relationships with the federal government, academic institutions, or industry. It is suggested that the PI, co-PIs, Study Chair, Operations and Steering Committee members, subcommittee members, and individuals named on the contract (including subcontractors and their staff) be required to complete annual COI forms. Once collected, the forms can be reviewed by registry staff and any conflicts forwarded to the Operations Committee for review. Any individuals that have a financial disclosure identified through the COI review process should declare it prior to participation in any scientific meetings, government meetings, presentations at sites, registry annual meetings, Steering Committee meetings, etc.

Informed Consent

The informed consent documents are key elements in determining the unique relationship between a patient's medical information and the ultimate use of this information in achieving the goals of the registry. The document must contain an explicit description of who will see what data and how confidentiality will be maintained. For registries with many partners as is common with public-private partnerships, it is desirable to have a common Informed Consent form. The Data Coordinating Center (DCC) for INTERMACS created an informed consent template in collaboration with the NHLBI that contains the necessary elements as determined by NHLBI and the institutional review board (IRB) at the DCC.

Evolution of Public-Private Partnerships

Registries that are public-private partnerships may undergo many changes over the lifetime of the registry. The registry goals and roles of stakeholders may change, and new stakeholders may become involved. Registries that are not initially set up as public-private partnerships may later evolve into PPPs.

The general topic of Registry Transitions is covered in a new chapter, but there are several changes and transitions that are unique to public-private partnerships.

For example, INTERMACS began as a collaboration between NHLBI, FDA, and CMS. The other partners currently involved in INTERMACS (and shown in Figure 2) joined later, and each brought their own agendas and goals for the registry. As these new partners joined, INTERMACS had to evaluate the many different goals they brought to the table, identify areas of overlap, and determine how INTERMACS could meet the needs of each partner while remaining focused on the ultimate goal of the registry: to improve patient outcomes.

Sometimes a registry is not initially organized as a public-private partnership and later evolves into one. This often happens when potential stakeholders do not see the value of being involved in a registry in the beginning stages, particularly when the registry has not yet published any results or provided proof of concept. In these situations, it is incumbent on the registry originators to operate the registry and produce results that will entice stakeholders to participate. For example, the Avian Flu Registry (funded by industry and operated by a private contract research organization) found much more success in partnering with international ministries of health after the Registry published its results in peer-reviewed journals and presented abstracts at well-known scientific conferences. Similarly, Get With The Guidelines was able to partner with state-level health departments only after consistently demonstrating its success in improving patient quality of care.

Considerations for Managing a Public-Private Partnership

Stakeholder Engagement

Once a public-private partnership has been established, it becomes critical to focus on proper management of the project. Major stakeholders may be involved, including clinicians, payers, patients/consumers, federal agencies, and industry/manufacturers. Inclusion of varying perspectives ensures balance, yet decision-makers from different sectors may have conflicting priorities. Engaging each of these groups with the common goal of improving health care quality and patient outcomes through sharing of data and other resources is vital to the achievement of the partnership. Such collaborations have occurred successfully in several industries where no single entity had the resources or expertise to drive an entire field.^{11,12} Eliciting trust among decision-makers combined with advice and/or participation from reputable associations are valuable incentives for maintaining the interest and engagement of collaborators.^{13,14,15} Successful collaborations satisfy the needs of multiple stakeholders,

providing immediate value and long-term returns, while driving innovation and efficient productivity and leading to the development of best practices.

Setting appropriate expectations for the participation of each group within the partnership is also vital. The utility of pre-project meetings involving discussion of priorities and policies that will govern the collaborative efforts cannot be overemphasized.^{16,17} Roles and responsibilities must be clearly defined and mutually agreed upon so that all stakeholders benefit equally.¹⁸ Evaluation of the available literature may reveal which practices have worked for other partnerships. Establishing guidelines that dictate partnership activities, including conflict of interest procedures, will allow accountability.^{19,20} Identification of a PI with strong leadership skills, a project manager to drive timelines, and other properly-trained team members will ensure successful execution of project goals.²¹ Agreement between participating groups on the time commitments required of them from the beginning will help set appropriate expectations. Resources that increase ease of communication and minimize time commitments, such as shared websites or databases,²² can speed development and improve participation. Although the importance of timelines is paramount, the ability to be flexible is also important in the changing landscape of healthcare policies and for public-private partnerships that add partners and collaborators and adapt over time.²³

Communication

Communication tools for generating and maintaining interest among stakeholders and participants are beneficial when used effectively. Initiation of interactive workshops or exchange forums between public and private sectors, dissemination of publications and news releases, and updates at professional meetings are all effective ways of communicating the necessary information to drive the partnership forward.²⁴ Periodic updates and exchanges of data have been shown to have positive effects on collaborations.²⁵ Overly frequent distribution of printed communications, required teleconferences, or excessive meetings will generate unwanted frustration or lack of continued support/participation. However, the value of a reasonable number of written updates, fairly regular calls (monthly, for example), and at least two in-person meetings (at onset and before distribution of results) are essential for building strong team morale, maintaining commitments, and achieving successful outcomes. Clearly these processes must be adapted to accommodate national and regional cultural sensitivities.

Visibility

Visibility of results and the breadth of dissemination of information obtained through the partnership should be discussed in the early planning phase of the project. Preparing results for wide dissemination requires considerable time and effort, which may not fall within the scope of the project team. However,

if such a distribution is desired and the funding and resources are available, the results can benefit a more widespread audience. Visibility of potential and perceived conflicts of interest should also be discussed at the onset of the partnership. An internal and/or external monitoring committee can reinforce ethical standards and trust among stakeholders.²⁶ The priorities involved with transparency and diffusion of information will depend on the nature of the partnership, the initial agenda, and the resources available.

Change Management

Anticipating and planning for change is good practice for all patient registries. Because of the nature of public-private partnerships and the variety of stakeholders involved, PPPs in particular may be more subject to changes in registry goals, stakeholders, budget, processes, and other areas. For this reason, it is important for PPPs to have a plan for how change will be managed. Tools that can assist in change management planning include a manual of procedures, a governing body, infrastructure for ongoing personnel training, and a plan for communicating change.

Protocols, governance and other related documents may change from time to time as a registry matures and adapts. Documents should be reviewed periodically and updated as needed. Re-submission for ethical review may be required, depending on the extent of the changes. The use of versioning (e.g., naming a protocol “Registry Protocol v1.0”) can reduce miscommunications and ensure that all stakeholders refer to the same document. It is also important to document major decisions that will affect the scope, budget, or otherwise impact the registry. For more information on managing change in registries, see the “Data Collection and Quality Assurance” chapter and the new chapter on “Registry Transitions.”

Special Considerations for International Public-Private Partnerships

International PPPs face some unique challenges, in addition to the usual challenges of language and cultural barriers. While some investigators may complain about the burden of compliance with regulation in developed countries, the opposite problem may exist in some less developed jurisdictions. The absence of a clear regulatory framework within which to operate may create problems in both the investigator’s home country and in the host collaborating country. One example may be lack of clarity in determining the responsible office for establishment of collaborations; another example may be changes in the local political landscape that alter this locus of responsibility. An issue that should be clarified in advance is the right to publish findings and to confirm the authorship. Early attention to these details will avoid later issues.

Key Factors for Success and Potential Challenges

Key Factors for Success

A PPP represents a valuable business model for the development of multi-stakeholder registries. The shared-risk and shared benefit nature of PPPs presents an ideal opportunity for attracting involvement from risk-averse elements in any sector, but these benefits coincide with challenges that may derail the success of a project as a whole.

A PPP starts with an identified public health issue in need of a solution. There is no shortage of strong, scientifically valid and important topics relating to the delivery of medical care and use of medical products; the challenge is in prioritizing these issues and focusing on pragmatic solutions for high-impact projects. For example, a registry tracking care patterns for a well-understood rare disease would likely generate less support than one that would collect acute and chronic data on a novel treatment for a highly prevalent condition. To ensure success of a given PPP, it is vital to communicate with a broad array of stakeholders early in the process to assure that the problem is appropriately conceptualized and that the goals mesh with priorities of stakeholders.

While PPPs represent a variety of interests and viewpoints, the value of a strong leader cannot be overstressed. Because of the nature of professional life, few people have the necessary time to devote to the difficult task of managing not only the scientific aspects of developing a registry, but also the equally challenging task of developing and managing an interdisciplinary team with diverse interests toward a common goal. The presence of a trusted and dedicated individual who is willing to commit substantial time to the development of a PPP is critical to the success of the project. This individual needs to be a recognized expert voice and have skills as a moderator, mediator, business developer, and salesman. Individuals who are open to pragmatic approaches that accommodate stakeholders without sacrificing the scientific integrity of the project will have a high likelihood of success. Similarly, an active and dedicated core team that represents an array of stakeholders is also necessary to support the goals of the PPP.

Many PPPs, like any project, are started with small conversations that grow into grand ideas. The formative stages of a PPP involve many steps of developing and refining the issues and potential solutions long before the first data entry form is ever filled out, and often consist of preparing documents, attending calls, holding workshops, and other collaborative activities. While talk is indeed cheap, there comes a point where the project cannot move further without some substantial funding. It is good practice to begin development of a funding strategy early, often alongside the development of the scientific strategy. Funding options should not depend solely on any one source or sector. This approach

broadens the base of support, making it more likely to be a sustainable funding model, while having the added benefit of potentially reducing the appearance of conflicts of interest.

If one views the PPP as a business model, the necessity to provide accurate and timely reports to shareholders becomes more readily apparent. In the planning process and throughout the development of the project, it is important to set goals and produce meaningful deliverables within a reasonable time frame. Projects that appear to drag on, or that have a dearth of outputs for an extended period are likely to lose support and jeopardize funding. Likewise, reporting of the progress of a project is critical to sustain interest and support. For PPPs that involve professional or academic societies, the annual scientific sessions of these organizations often provide an ideal opportunity to update the community.

Clear communication in open forums that encourages and allows for buy-in and feedback is another critical component to ensuring success in a PPP environment. A registry is a unique application of the PPP model in that successful implementation of the final project is heavily dependent on individual hospitals and practitioners. Having stakeholders represented at the leadership levels of organizations is necessary for good governance; however, communicating with the physicians, hospitals, nurses, and associated staff to address their concerns will promote enrollment. Further, the case must be made to this group that the registry will add value to their organizations, and not just represent a further drain on their already sparse time.

Some registry characteristics that increase the probability of success include:

- The registry should have goals that address a clear and current clinical need in a well-defined population. These goals become the rallying point for the diverse partners.
- The expectations of each partner should be explicitly enumerated, pragmatic, and measurable.
- The registry should return value to all partners who are financial contributors. As much as possible the value should equal or exceed the financial contribution for each partner.
- The registry should have strong, respected leaders who have national or international reputations.
- High quality data is essential to the success of the registry. Protocol-driven efforts to assess compliance with the registry protocols and well-defined efforts to repair any deficient areas are critical.
- While the registry should be built for consistency, it still must have an element of flexibility to allow it to react to changes in the clinical landscape.

Common Challenges

The first challenge is to create a structure and protocol that is realistic and will capture the data necessary to meet the goals, but flexible enough to accommodate change when necessary. The second challenge is to follow the protocol on a daily basis. The third challenge is involving partners in developing and implementing the registry structure. If a registry is successful, many spin-off projects and additional uses of the registry may appear. Maintaining focus on the original goals of the registry while responding to increasing registry demands is clearly a challenge. Creating a business plan that will allow for sustainability of the registry is one of the biggest challenges. Assessing quality of life and other patient-reported outcomes, including clinical assessments (e.g., neurocognitive assessment) is a challenge because direct interaction with the patient is required. The biggest challenge is to provide daily high level effort that simultaneously focuses on regulatory and data quality issues while continuing the scientific mission of the registry.

Conclusions

Public-private partnerships are increasingly being used as a model for operating patient registries in the U.S. and internationally. Government regulators and payers are increasingly requiring evidence development to inform decisions about approval, coverage, and expanded indications, and patient registries governed by public-private partnerships are in a unique position to fulfill those requirements. In the future, PPPs that include international partners will continue to be important. While there are special considerations for planning and operating public-private partnerships, they offer a unique way for varied stakeholders to contribute their particular strengths to achieve a common scientific goal.

References

- ¹ Food and Drug Administration Amendments Act of 2007. Available at: http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110. Accessed August 10, 2011.
- ² Dreyer NA, Starzyk K, Wilcock K, Toovey S. A global registry for understanding clinical presentation, treatment outcomes, and survival from human avian influenza. Bangkok International Conference on Avian Influenza. 2008 Jan 23; Bangkok: National Center for Genetic Engineering and Biotechnology; p. 155, 2008.
- ³ Adisasmito W, Chan PKS, Lee N, Oner AF, Gasimov V, Aghayev F, Zaman M, Bamgboye E, Dogan N, Coker R, Starzyk K, Dreyer N, Toovey S. Global Patient Registry for Influenza A/H5N1: Strengthening Results using Multiple Imputation. XIII International Symposium on Respiratory Viral Infections. Rome, Italy, 13-16 March 2011.
- ⁴ Adisasmito W, Chan PKS, Lee N, Oner AF, Gasimov V, Aghayev F, Zaman M, Bamgboye E, Dogan N, Coker R, Starzyk K, Dreyer NA, Toovey S. Effectiveness of antiviral treatment in human influenza H5N1 infections: analysis from a global patient registry. *J Infect Dis*. 2010 Oct 15; 202(8): 1154-60.
- ⁵ Adisasmito W, Chan PKS, Lee N, Oner AF, Gasimov V, Zaman W, Bamgboye E, Dogan N, Starzyk K, Dreyer NA, Toovey S. Strengthening Observational Evidence for Antiviral Effectiveness in H5N1. *J Infect Dis* 2011 204: 810-811.
- ⁶ Schwamm L, Fonarow G, Reeves M, et al. Get With the Guidelines -Stroke is associated with sustained improvement in care for patients hospitalized with acute stroke or transient ischemic attack. *Circulation* 2009; 119:107-11.
- ⁷ Centers for Medicare & Medicaid Services. National Coverage Determinations with Data Collection as a Condition of Coverage: Coverage with Evidence Development: Guidance for the Public, Industry, and CMS Staff. 12 July 2006. Available at: <https://www.cms.gov/medicare-coverage-database/details/medicare-coverage-document-details.aspx?MCDId=8&McdName=National+Coverage+Determinations+with+Data+Collection+as+a+Condition+of+Coverage%3a+Coverage+with+Evidence+Development&mcdtypename=Guidance+Documents&MCDIndexType=1&bc=BAIAAAAAAAAA&>. Last accessed on 20 September 2011.
- ⁸ Centers for Medicare & Medicaid Services. National Coverage Determinations with Data Collection as a Condition of Coverage: Coverage with Evidence Development: Guidance for the Public, Industry, and CMS Staff. 12 July 2006. Available at: <https://www.cms.gov/medicare-coverage-database/details/medicare-coverage-document-details.aspx?MCDId=8&McdName=National+Coverage+Determinations+with+Data+Collection+as+a+Condition+of+Coverage%3a+Coverage+with+Evidence+Development&mcdtypename=Guidance+Documents&MCDIndexType=1&bc=BAIAAAAAAAAA&>. Last accessed on 20 September 2011.
- ⁹ Lindsay MJ, Siegel BA, Tunis SR, Hillner BE, Shields AF, Carey BP, et al. The National Oncologic PET Registry: expanded medicare coverage for PET under coverage with evidence development. *AJR Am J Roentgenol*. 2007 Apr; 188(4):1109-13.
- ¹⁰ Hammill S, Phurrough S, Brindis R. The National ICD Registry: now and into the future. *Heart Rhythm*. 2006 Apr; 3(4):470-3.
- ¹¹ Reich MR, ed. *Public-Private Partnerships for Public Health*. Cambridge, MA. Harvard Center for Population and Development Studies; 2002:205.
- ¹² Nikolic IA, Maikisch H. Health, Nutrition and Population (HNP) Discussion Paper. *Public-Private Partnerships and Collaboration in the Health Sector. An Overview with Case Studies from Recent European Experience*. Washington, DC. The International Bank for Reconstruction and Development/The World Bank; 2006:27.
- ¹³ Wagner JA, Prince M, Wright EC, et al. The biomarkers consortium: practice and pitfalls of open-source precompetitive collaboration. *Clin Pharmacol & Ther*. 2010; 87(5):539-542.
- ¹⁴ Goodman M, Almon L, Bayakly R. Cancer outcomes research in a rural area: a multi-institution partnership model. *J Community Health*. 2009; 34:23-32.
- ¹⁵ Omobowale EB, Kuziw M, Naylor MT, Daar AS, Singer PA. Addressing conflicts of interest in public private partnerships. *BMC Internat Health & Human Rights*. 2010; 10:19.
- ¹⁶ Nishtar S. Public-private 'partnerships' in health – a global call to action. *Health Research Policy and Systems*. 2004; 2:5.

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- ¹⁷ Bloom GS, Frew D. Regulation of research through research governance: within and beyond NSW health. *NSW Public Health Forum*. 2008;19(11-12):199-202.
- ¹⁸ Ciccone DK. Arguing for a centralized coordination solution to the public-private partnership explosion in global health. *IUHPE – Global Health Promotion*. 2010;17(2):48-51.
- ¹⁹ Ciccone DK. Arguing for a centralized coordination solution to the public-private partnership explosion in global health. *IUHPE – Global Health Promotion*. 2010;17(2):48-51.
- ²⁰ Omobowale EB, Kuziw M, Naylor MT, Daar AS, Singer PA. Addressing conflicts of interest in public private partnerships. *BMC Internat Health & Human Rights*. 2010;10:19.
- ²¹ Wagner JA, Prince M, Wright EC, et al. The biomarkers consortium: practice and pitfalls of open-source precompetitive collaboration. *Clin Pharmacol & Ther*. 2010;87(5):539-542.
- ²² Wagner JA, Prince M, Wright EC, et al. The biomarkers consortium: practice and pitfalls of open-source precompetitive collaboration. *Clin Pharmacol & Ther*. 2010;87(5):539-542.
- ²³ McKee M, Edwards N, Atun R. Public-private partnerships for hospitals. *Bulletin of the World Health Organization*. 2006;84(11):890-894.
- ²⁴ HIV-related Public-Private Partnerships and Health Systems Strengthening. Geneva, Switzerland. Joint United Nations Programme on HIV/AIDS (UNAIDS); 2009:32.
- ²⁵ Goodman M, Almon L, Bayakly R. Cancer outcomes research in a rural area: a multi-institution partnership model. *J Community Health*. 2009;34:23-32.
- ²⁶ Omobowale EB, Kuziw M, Naylor MT, Daar AS, Singer PA. Addressing conflicts of interest in public private partnerships. *BMC Internat Health & Human Rights*. 2010;10:19.