REVIEW ARTICLE

A systems approach to enhance clinical research and medicines development

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Abstract: The biopharmaceutical industry has traditionally been the key link between basic biomedical discovery and novel medicines. Today, the industry faces numerous challenges including the broad agreement that the current clinical trial system is inefficient and flawed. Most challenges are worsened by the inability of the stakeholders to work collaboratively. Over the last decade, many cooperative efforts to transform clinical research have been launched, but a systemic solution has not been envisioned. A systems approach, including the application of systems engineering principles, has been used in other sectors and proposed for use in healthcare and medicines development. Clinical research, when looked at in systems terms, can be defined as an open system involving patients, investigators and associated staff, regulators, sponsors and stakeholders interconnected through a series of processes to bring effective and safe medicines into the market. ACRES is a global nonprofit organization with a mission of creating a multi-sector alliance of individuals and institutions collaborating on building a shared global system for clinical research excellence. A fundamental element of the ACRES system includes a global network of high-performing research sites interconnected through a shared information technology platform, with standardized policies and operational procedures and a robust, secure database to support performance, quality and safety. Five core initiatives address the larger mission and are currently ongoing. Deliverables will roll out over 2015–2018. Positive reception to the concept, vision and goals among critical stakeholders, and a steady influx of strategic allies willing to work collaboratively demonstrates the strong pull exerted by the vision of a global system. However, due to the undertakings' scope and complexity, challenges remain. Recognition that effective shared collaboration is the best long-term option among stakeholders and the general public constitutes a powerful incentive for ACRES contributors and strategic allies to keep working and make it happen.

Keywords: clinical research, systems approach, site accreditation, core competencies, shared information technology platform

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1. Introduction: Why is a Systems Approach Needed?

The biopharmaceutical industry has traditionally been the key link between basic biomedical discovery and the emergence of novel medicines. Today, the industry faces a number of ongoing and emerging challenges, including technical knowledge gaps, limitations in clinical testing, lowered productivity, higher development costs, increased regulatory requirements, growing payer pressures, patent expiration and an overall lack of openness and public

trust[1–4].

Most large biopharmaceutical companies are compensating for this by shifting to alternatives such as mergers and acquisitions of other, often smaller, companies, outsourcing, and fixed cost and personnel reductions, as well as broader collaboration with academia, contract research organizations and nonprofit institutions. An increased focus on growing new and emerging market revenue streams, including personalized medicine and rare diseases, is also surging. A more prominent role for the patient in designing research and implementing trials is under discussion in many ways. Countries from the emerging world are increasingly involved in the global medicines development process, and this is reflected in the climbing number of publications and data supporting regulatory submissions worldwide. In terms of technological solutions alone, local and regional enterprises are also blooming[4,5].

Clinical trials constitute the largest single component of the R&D budget of the biopharmaceutical industry, representing nearly 40% of the R&D expenses of major companies. However, there is broad agreement that the current clinical trial system is inefficient at best, and deficient and wasteful in other regards[6].

Currently, each clinical trial is typically organized *de novo*, requiring substantial effort, cost, and time. Sponsors and contract research organizations (CROs) must identify clinical investigators and assemble multi-investigational teams. Protocols must be written, approved by regulators and submitted to each of many institutions, where approval by ethics committees and contract negotiators can take several months, without necessarily improving the scientific and ethical aspects of the study or the protection of study participants. A wealth of published research details the inefficiency in the clinical research process. A recent evaluation by the Institute of Medicine[7] assessed the challenges affecting the US clinical trials enterprise including:

- Increasingly high costs, lengthy delays and inconsistencies associated with elaborate administrative procedures established by risk-averse research organizations;
- Decline in the number of medical researchers, coupled with the lack of stable funding and employment;
- Low rates of enrollment and retention of people in clinical trials coupled with lackluster recruitment efforts by physicians and other healthcare providers, so that many planned trials are not completed;
- Inconsistent adoption of clinical trial results by healthcare providers, payers and patients in making decisions related to individual patient care.

On the other hand, the most common deficiency codes reported by the US FDA following clinical investigator site inspections are *Failure to follow investigational plan* and *inadequate and inaccurate records*[8]. About one out of three investigators do not adhere to the investigational plan and one out of four investigators do not keep accurate records. There has not been any improvement in these findings for more than two decades[9].

Thus, errors are repeated time and time again in research across the world with poor organizational learning and much wasted effort.

The lack of an adequately sized and appropriately trained multi-professional workforce both in the industry and in the clinical research field is also a significant part of the problem. Larger pools of highly trained, competent professionals are needed to increase the industry's ability to safely and effectively bring new medicines to the marketplace. The necessity for further competency based education and training has been identified all over the world[10–14].

Many of the challenges outlined are worsened by the inability of the biopharmaceutical industry, governments and regulatory agencies, academic researchers, and the healthcare community to work together collaboratively. This makes it difficult to fill these gaps and create not only effective clinical trial professionals but also powerful networks and realistic trial designs.

Over the last decade, many collaborative efforts to transform clinical research have been launched, but a systemic solution has not been envisioned. Each initiative—including the Clinical Trials Transformation Initiative[15] the European Innovative Medicines Initiative[16], the Multi Regional Clinical Trials Initiative (MRCT)[17], CDISC[18] and most recently TransCelerate[19] was designed to address one specific aspect of the clinical trial chain rather than the entire endeavor.

Therefore, it is self-evident that a comprehensive, high-performing system that integrates key stakeholders on a sustained basis has been regarded as necessary[7].

2. What is a Systems Approach?

A systems approach, including application of systems engineering principles and thinking, has been used in other sectors ranging from transportation and defense to energy, electronics and information technology. These sectors recognized long ago the value and importance of systems thinking and have effectively applied it beneficially in their respective domains. Likewise, the concepts of systems, systems approaches and systems engineering have been proposed as possible solutions to address complex problems in public health[20] and drug discovery and development[21,22]. Despite well-intentioned patchy efforts, systematic application has not occurred.

An analogy to the airline transportation system is among the easiest to understand as it encompasses everything from scheduling, reservations, flight logistics and baggage-handling to air traffic control, communications, financial management and regulatory simplification.

Every system is delineated by its spatial and temporal boundaries, surrounded and influenced by its environment, described by its structure and purpose and expressed in its functioning. Some systems share common characteristics[23] including:

- Structure: it contains parts (or components) that are directly or indirectly related to each other;
- Behavior: it exhibits processes that fulfill its function or purpose; and can be categorized as either fast or strong, as related to its surroundings;
- Interconnectivity: the parts and processes are connected by structural and/or behavioral relationships.

The term "systems thinking" denotes a methodology applicable to a wide range of endeavors. Basically, systems thinking focuses on interactions and interdependencies that together define an integrated whole, from control points to communications. These are viewed from the perspective not only of technology but human behavior—the "hard" and the "soft" dimensions, as it were. But most fundamentally, a systems approach is the diametric opposite of "silos"—the fragmentation of operations, functions, and stakeholders acting in isolation, so typical in biomedical R&D and healthcare, under a misguided reductionist approach[23].

A feature common to systems thinking is leveraging data-rich environments to probe their complexities and create integrating solutions that cut across operations, functions, and stakeholders. The key properties of a system, compared with each of its elements or parts, are its emerging patterns and behavior[23].

Systems thinking is an approach to problem solving, viewing: "problems" as parts of an overall system in contrast to isolating specific parts, outcomes or events that result in further, and unintended, consequences. Systems thinking is a framework that is based on the understanding that the component parts of a system can best be understood in the context of relationships with each other and with other systems, rather than in isolation. Systems thinking focus on the cyclical and dynamic, and on feedback mechanisms, rather than on linear and static cause and effect[24].

Clinical research in medicines development can be defined as an open system involving patients, investigators and associated staff, regulators, sponsors, research sites, and so on as components interconnected through a series of processes that aims to introduce and maintain effective and safe medicines in the market. In effect, all who work in clinical research have a defined role which influences the system sometimes in ways many do not realize.

A sound "systems approach" is thus needed to bring together all of the stakeholders involved in clinical research to identify and strengthen the interconnections among component parts, improve the attendant processes, and enhance transparency across the system. This in turn will help to overcome the current barriers to cost-effectiveness, efficiency, safety and ethical behavior impacting decision-making at all levels and appropriate management of risks.

3. What is ACRES?

ACRES (Alliance for Clinical Research Excellence and Safety) is a multi-sector alliance of innovation-minded individuals and organizations working collaboratively to build a shared global system for clinical research excellence. ACRES is a global non-profit organization operating in the public interest based in Cambridge, MA, USA.

Currently, it involves over 60 strategic allies that are committed to change. ACRES allies include not only sponsors and CROs, but also academic institutions, professional associations and societies, technology vendors, service providers, ethics committees, research site networks, patient groups and cross-sector collaborations. Such a unique alliance has never been established before.

In addition, well over 90 executives, senior managers, and subject matter experts from all over the world participate in the range of ACRES Foundation Initiatives (such as Site Accreditation and Standards, Safety, and Technology Integration), working together to achieve the ACRES vision by applying effective systems thinking to the clinical research enterprise in the spirit of volunteerism.

One level of the ACRES integrated system for clinical research envisions a global network of high-performing research sites interconnected through a shared information technology platform, with standardized policies and operational procedures and a robust, secure database to support mission-critical analysis of performance, quality and safety within an enterprise-wide culture of safety (Figure 1).

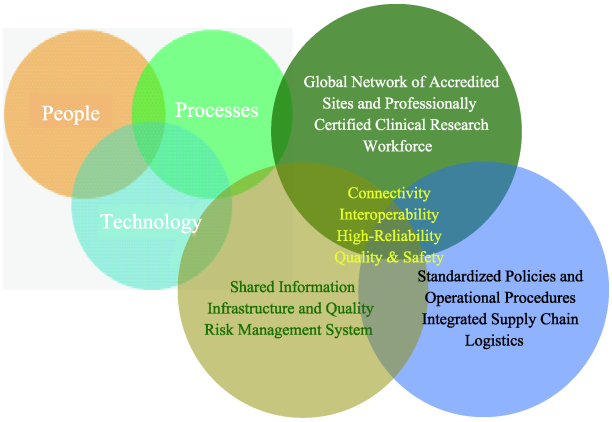

Figure 1. The Core concept of ACRES (cite from www. acres-global.net).

Such an integrated system operates under the premise of Accountable Research™, complementary to Accountable Healthcare, which implies the development, recognition and acceptance of principles of individual and organizational social responsibility for conducting biomedical research in a manner that assures the interest and well-being of research subjects, the safety of therapeutic products, the integrity of all research data and the effectiveness of operational processes to benefit all stakeholders worldwide.

The ACRES mission has anticipated four essential domains: site development, support and sustainability, quality and safety management, safety and pharmacovigilance, and information technology. Projects and objectives were devised within each of the operational domains leading to the five Foundation Initiatives, each with specific goals, deliverables and timelines.

An overview of ACRES Foundation initiatives and some initial deliverables follows. It is important to emphasize that they are integrated, that is, each impacts the others as a reflection of the systems thinking approach.

4. ACRES Foundation Initiatives

Five core initiatives are currently underway:

- Site Accreditation and Standards (SASI)
- Site Optics and Quality Informatics (SOQI)
- Product Safety Culture (PSCI)
- Global Ethical Review and Regulatory Innovation (GERI)
- Quality Assurance and Safety (QASI)

Site Accreditation and Standards (SASI): Site accreditation and certification of the clinical research teams are key elements for Accountable Research™. This initiative addresses the need for a cohesive, effective approach to promoting and sustaining excellence of clinical research sites.

Currently, uniform standards for clinical research sites and independent third-party accreditation do not exist. Yet such standards are required to objectively assess and recognize sites of excellence and to ensure their sustainability. The burgeoning costs of conducting clinical trials include inefficiencies that partly result from the lack of uniform standards and accreditation support infrastructure. Uniform standards further ensure connectivity and interoperability essential to establishment of an effective global network.

The implementation of SASI is now in its third phase. The first phase surveyed the current landscape and gathered perspectives from a wide range of stakeholders from the USA, Europe, Asia and Latin America. Seven standard domains were identified: personnel, facilities, management, information technology, quality management, research integrity and patient engagement. The specific standards pertaining to each domain are currently under preparation and a pilot test will follow. The final standards are to be available by December 2016.

Related ongoing projects within SASI or impacting SASI as part of the ACRES collaboration with other strategic allies include:

- *Development of harmonized core competencies for clinical research professionals* in collaboration with a range of professional associations and academic institutions gathered under the Joint Task Force for Clinical Trial Competency[11]. The core competencies are to be used for

the accreditation of postgraduate education and training programs as well as to define job portfolios and job profiles. An international validation exercise is currently ongoing.

- *Preliminary identification of levels of sites* as related to the complexities required of the various phases of clinical trials (Table 1). A validation process would be developed in alignment with SASI phase III.
- *Creation of a "universal" developmental model of electronic data flow* mapping clinical trial information exchanges (from trial design through regulatory approval). The project also promotes a comprehensive integration of the model into operational systems at all levels of the health sciences and medicines development enterprise.
- *Development of a "trust framework" within the global system to ensure a secured information exchange*: The pilot experience with strategic allies has been completed.
- *Development of a "menu" of ally-provided site services to support standards adherence and accreditation and to promote operational excellence and sustainability.*
- *Development of a neutral third party accreditation oversight entity* to oversee and "authorize" accrediting bodies, since ACRES will not be an accrediting body. This recognizes that different countries have, or will have, various accreditation approaches (some governmental, some private, and some a combination). Accreditation of as many as 150,000 sites globally will likely require multiple accrediting entities, each of which themselves will require accreditation to ensure the integrity and effectiveness of the accreditation process. The accreditation entity would be the custodian of the standards and house the process for accreditation.
- *Creation of an innovative "dynamic accreditation" process:* different from traditional accreditation models, this approach analyzes real-time performance, quality, and safety data according to established metrics to determine whether a site is operating in a manner consistent with the accreditation standards, optimizing performance and regulatory and ethical compliance. Dynamic accreditation utilizes information generated during the routine clinical trials process, largely eliminating administrative burdens attendant to most accreditation processes while improving timeliness and effectiveness.
- *International expansion,* through the appointment of country and regional coordinators

Table 1. Minimum criteria for site qualification

Parameter	Site Level I	Site Level II	Site Level III	Site Level IV
Studies conducted	PMS/PASS/Comparative effectiveness	Phase IV or Phase IIIb	Phase II-III Investigator initiated	Phase I-III IIS
Study end-points	Patient reported Laboratory Surrogate markers	Level I + Novel biomarkers	Level II + Not validated biomarkers	Level III + Exploratory biomarkers
Number and complexity of Procedures/Protocol	Few	Intermediate	High	High/very high/Proof of Concept
Expected safety profile	No specific safety issues/ Well known AE profile	Level I + Unknown SAEs	Level II + Unknown AE/SAE	First in humans Unknown SAEs/AEs
Study duration	Days to months	Weeks/Months	Days to months	Days to months
Patient demographics	Outpatients	Outpatients/Inpatients	Outpatients/Inpatients	Out and inpatients
Average # of studies conducted/year	<5	<10	<15	>15
Site technological facilities	Few; standard of care AQ (Standards/Standard)	Few; standards of care	Level II + advanced technologies	Advanced technologies Genomics
IT communication facilities	Acceptable	Acceptable	Good	Excellent
Expertise in diverse medical specialties	Single	2–3 medical disciplines	Several (5–10)	>10
GCP compliance in the past 5 years	<1 audit	<3 audits and no critical audit findings	< 5 audits and no critical audit findings	>5 audits and no critical audit findings
Investigator and staff certification	No	No	Yes	Yes
Emergency medical care available	No	Yes	Yes	Yes

committed to creating awareness of the ACRES new system and helping in the creation of the country site networks. Activities include the local site identification, recruitment and affiliation as well as interface with the country regulatory agencies. An ACRES organization is already operative in Japan, and frameworks are being established in Korea, Germany and Bulgaria, among other countries (see www.acresglobal.net).

Site Optics and Quality Informatics (SOQI): This initiative addresses the need to ensure interoperability across the global network of sites and to optimize application and exploitation of technology. In addition to standards, the system will require a robust and supportive information technology platform that can be shared on an enterprise-wide basis. The following infrastructure projects are underway:

- *Creation of a Technology Consortium,* aimed at developing a shared, universal interface engine that will allow sites, sponsors, contract research organizations, regulators, other providers of products and services as well as patients to communicate and collect, archive and share information in a secure manner. The partners of the consortium are currently developing models and technical specifications, seeking to complete the initial application for testing and evaluation by the end of 2015, with anticipated deployment in 2016.
- *The ACRES BlueCloud* which allows the access and management of information in real time from multiple sources through application program interfaces (APIs). In short, it is an integration system that allows healthcare and clinical research providers to consolidate and deliver information in real time from a common, secured, compliant and industry-neutral single location for the purpose of Accountable Research™. The timelines run in parallel to the consortium's.

Product Safety Culture (PSCI): This initiative explores the application of safety engineering, human factors, and organizational science insights, tools, and techniques to design safe systems for clinical research with a particular focus on training and education. In addition, it is examining better pharmacovigilance practices not covered by any guidelines or regulations. Primary projects are underway that integrate with other ACRES efforts, including:

- Using a model of causation (STAMP or Systems-Theoretic Accident Model and Processes) to investigate whether and how it might improve the design, operation, and management of the subsystem for early phase pharmacokinetics and pharmacodynamics research including trials (Phase I). This may help in creating a common roadmap for safe early development using safety engineering methods and applying insights from the emerging interdisciplinary field of Human Factors which focuses on how psychological dimensions impact making judgments and decisions.
- By working with IT allies, promoting creation of a unified safety database whereby all datasets relevant for patient safety will be integrated through an open access clinical research safety informatics subsystem.
- Establishing standards for safe and effective outsourcing in pharmacovigilance.
- Public outreach in cooperation with media outlets and other organizations, focused on interactive education and training of the public and journalists reporting on biomedical research by discussing safety-related matters and other key issues related to clinical trials and health with the general public. An Accountable Research blog has been created in cooperation with Hearst Media (http://blog.mysanantonio.com/acresaccountableresearch/2015/04/accountability-in-health-health-care-and-biomedical-research/).

Global Ethical and Regulatory Innovation (GERI): This initiative addresses the need for ethical and regulatory global standardization (beyond 'harmonization'), the difficulties in complying with complex regulations and guidance and the need for leveraged interaction between regulators and other key stakeholders to support innovation and build trust. Many agree that the needs of patients should dominate all activities ('patient-centricity') although how that should happen is unclear. The following initial projects are underway:

- Mapping global efforts for regulatory simplification and innovation and deriving implementable solutions from ethical and efficiency perspectives beginning with development of a glossary and focusing on informed consent in the first in a series of a multi-stakeholder symposium

consultations.

- Following agreement on guiding systems principles for informed consent, extrapolating and establishing these to ethical and regulatory needs for globally accredited research sites, and aligning standards for optimizing transparency and increased trust in communication and cooperation among stakeholders related to SASI and PSCI.

Quality Assurance and Safety Initiative (QASI): This initiative include methods for remote risk-based monitoring and audit sharing as well as addressing the unique needs of alternative forms of conducting clinical trials in light of scientific discoveries, such as development of genomics and proteomics, and personalized medicine's impact on clinical research. Creation of a single repository of audit findings will contribute to organizational learning.

5. ACRES Impact, Challenges and Opportunities

ACRES was incorporated as a nonprofit organization in 2012, although the original concept dates to over a decade prior. This timing was on target, based on the accumulation of needs globally, and recognition by biomedical R&D stakeholders and critics.

ACRES has had a favorable reception to its concept, vision and goals among critical stakeholders including regulatory agencies, pharmaceutical companies, academic sites, professional organizations, technology providers and the public. A steady influx of strategic allies willing to partner and volunteer to help achieve the ACRES vision and collaborate in devising the system is ongoing, and is further evidence of the timing being appropriate (Figure 2).

Differing in intent from trade associations, professional societies, and other forms of nonprofit organizations is also an important dimension of ACRES's broad-based and growing acceptance.

Nevertheless, given the scope and complexity of its undertaking, challenges remain in constructing the global system as visualized by the ACRES vision, in particular:

- Conveying the conceptualization of the system and its parts in contrast to what currently exists and overcoming organizational inertia, apathy and resistance to change.
- Demonstrating the feasibility of building such a system in an effective and efficient manner in a time of scarce resources and changing regulations.

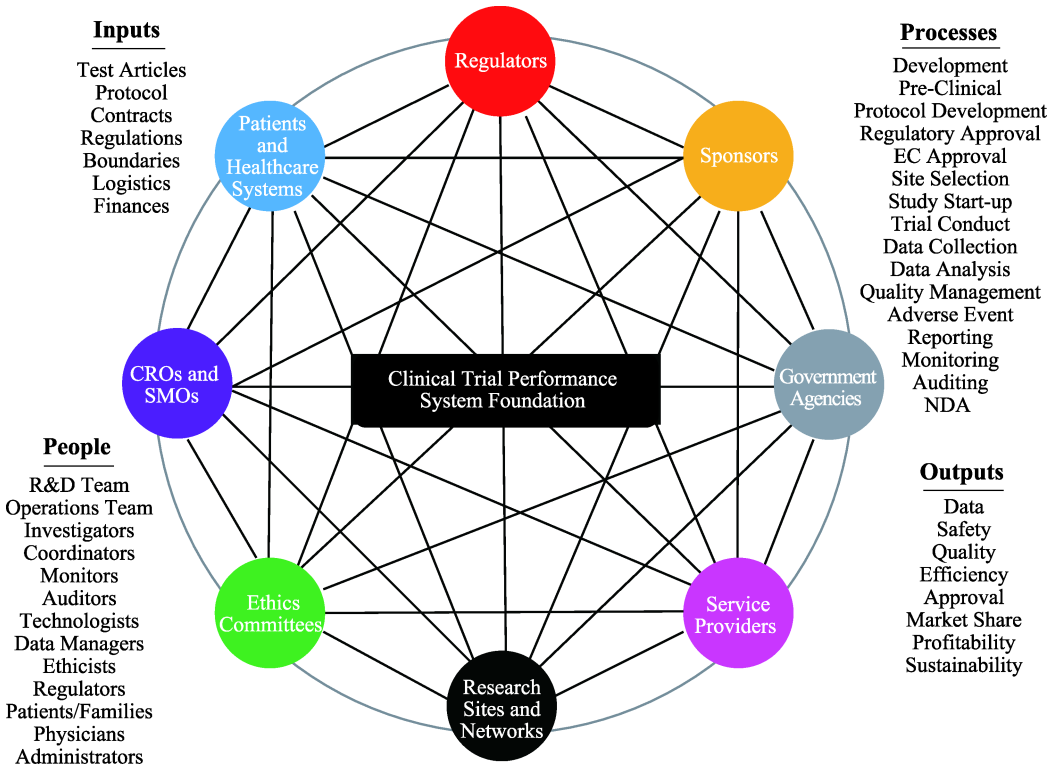

Figure 2. The components of the ACRES system.

- Expanding the visibility and clarity of the ACRES message among and across the multiple stakeholders.
- Continuing to generate sufficient resources, both financial and in-kind, to support mission critical initiatives and the basic ACRES infrastructure to supplement the significant volunteer and donor resourcing that ACRES has enjoyed from inception.
- Confusion with other initiatives that could be seen as competing or overlapping, leading to ACRES being perceived as redundant even though ACRES itself is unique. Recent benchmarking — as well as meetings with a range of such initiatives—has proven valuable for all parties, ensuring both the value of and best areas for cooperation, something ACRES is striving to accomplish[25].

Ways of overcoming these challenges continue to evolve and thus ACRES continues to gain multi-stakeholder support. No less significant, ACRES presence and efforts have had a positive impact on other reform efforts, including both adoption and adaptation by specific stakeholder groups as part of their own respective missions (but independent from an overall intended system as yet). In addition, there is no downside or negativity so long as ACRES remains focused on science and patients' needs because ACRES is committed to learning from all of its experiences.

ACRES has also worked diligently to establish relationships with national regulatory agencies as well as with pharmaceutical companies and global professional associations, since endorsement and acceptance by these constituents are critical for the sustainability of the proposed system.

From the economic perspective, the case for a global system approach is solid and self-evident. Estimated gains in efficiency, time to market, clinical trial performance, safety, regulatory burden, and reduced waste can reach several billions of dollars. Already, organizations using just small parts of the ACRES BlueCloud are realizing that millions of dollars in savings can be achieved, but further pilot and confirmatory experiences will be necessary once the foundations of the system are in place.

The ACRES model for a financially self-sustaining organization is based on a range of revenue streams related to the products and services of the Foundation Initiatives.

Deliverables from the various ACRES Initiatives are anticipated during the period 2015–2018. Pilot testing for implementation is an essential part of the process for assuring integration into the planned system.

Engagement with research sites is critical and thus efforts for recruitment and qualification will be a primary objective in the short term as part of a staged implementation plan leading to the formal site accreditation in the medium term.

Implementation of ACRES is indeed a complex and challenging undertaking and significant anticipated obstacles are being addressed. Realization that an effective shared collaborative system is the best long-term option among stakeholders and the general public constitutes a powerful incentive for the ACRES contributors and strategic allies to keep working to make it happen. The need to demonstrate leadership and restore passion into clinical research has never been greater.

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No conflict of interest was reported by the authors.

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