21st Century Cures: A Call to Action

Statement of the Association of Clinical Research Organizations

June 13, 2014

Summary of Recommendations for Congressional Action

In the statement to follow, ACRO identifies and offers recommendations for Congressional action across several broad topics:

I. Ensuring that the United States Remains Globally Competitive in Clinical Research

- Reduce the silo-ing of government, private sector and academic research initiatives. Specifically, **Congress should direct that the National Center for Advancing Translational Sciences (NCATS) of the NIH and the Patient Centered Outcomes Research Institute (PCORI) actively engage private-sector resources and expertise**, including the member companies of ACRO, in areas such as the development of data and research networks, project management, data management, trial design and feasibility, patient recruitment and the like.

- **Make the R&D tax credit permanent, simplify it, and extend a portion of the benefits currently not utilized to incentivize the conduct of clinical trials in the US**.

II. Unlocking EHRs and Other Big Data Sources

- **Congress should encourage inclusion of new EHR (electronic health record) functionalities** that will facilitate clinical and data-driven research **as part of the ONC/CMS Meaningful Use Phase 3 requirements**, including connectivity between clinicaltrials.gov and EHR systems to facilitate clinical trial recruitment.

- **Congress should amend HIPAA to define data research as part of health care operations at 45 CFR 164.506** in order to allow the use of protected health information for non-interventional studies.

III. Driving Innovation at the FDA

- **Engage the GAO or other 3rd party to review and prepare a report answering questions such as:** Is the FDA, an agency with scarce resources, receiving an adequate return on its investment in the Clinical Trials Transformation Initiative (CTTI) and similar public-private collaborations intended to produce "transformational" outcomes? Should the agency consider reallocating these funds toward additional investment in regulatory science or an increase in review staff?

915 15th Street, NW, 2nd Floor, Washington, DC 20005
T 202 464 9340 E info@acrohealth.org www.acrohealth.org

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ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

- **Direct that the FDA appoint a Chief Innovation Officer** who shall be responsible for overseeing the Critical Path Initiative and will have the authority to agree to and enforce new, innovative approaches to drug development.

Background

The Association of Clinical Research Organizations (ACRO) represents the world's leading global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from discovery, pre-clinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. With more than 100,000 employees engaged in research activities around the world, ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research. CRO industry revenue is expected to reach $23.6 billion for 2014, representing well over one-third of *development* spending.

Each year, ACRO member companies conduct more than 11,000 clinical trials involving nearly two million research participants in 115 countries. On average, each of our member companies works with more than 500 research sponsors annually, and we have a broad and unique understanding of the roles, responsibilities and behavior of all the stakeholders – research sponsors, investigators, Institutional Review Boards, clinical trial participants and ancillary providers of all types – that are part of the research enterprise.

As the Energy and Commerce Committee is well aware, the current methodology for medical product development in the United States is unsustainable, taking far too long (from 10-15 years,) and far too much investment (from a low estimate of $350 million to an amortized cost across a full development portfolio of up to $5 billion) to produce a single new drug or biologic. Up to 80 percent of that time and cost is spent in *preclinical* (laboratory and animal testing) and *clinical development* (phase 1, 2 and 3 clinical trials) the parts of the development paradigm that CROs specialize in. Drug development is a complex and multi-faceted effort, requiring capabilities ranging from toxicology and pharmacology to clinical trial management, and ACRO member companies are focused on creating new technologies and business processes to address the time-and-cost conundrum, while at the same time improving the quality and efficiency of the clinical development enterprise.

ACRO applauds the "21st Century Cures" initiative and believes that a multi-stakeholder approach to identifying barriers and creating solutions to our toughest healthcare challenges presents a genuine opportunity for aligning US science and technology capabilities with regulatory policy to benefit not only individual patients but our society as a whole. As companies that represent more than one-third of development spending and are involved in

the conduct of more than half of all clinical trials worldwide, we will focus our comments on pathways to facilitating a new learning and feedback loop across the *discovery-development-delivery* cycle, and potential ways for the U.S. Congress to encourage innovation.

Competing in the Global Innovation Environment

During the Committee's initial Roundtable, one of the topics of discussion was the question of what the U.S. can learn from the policies and incentives being used by other countries to encourage biomedical investment and development innovation. In terms of a public-private partnership that aims to take bold action to accelerate the drug development process, we commend for the Committee's consideration the Innovative Medicines Initiative (IMI,) a joint project of the European Union and the member companies of the European Federation of Pharmaceutical Industries and Associations (EFPIA). With a €1 billion Euro contribution from the European Commission and matching (mostly in-kind) contributions from EFPIA, IMI is building research networks and undertaking collaborative research projects to boost innovation in healthcare. The IMI aims to remove bottlenecks in drug development, encourage pre-competitive data sharing and research, and build new business models based on collaboration.

One IMI project, with a budget of over 16 million Euros, EHR4CR (Electronic Health Records for Clinical Research) is building standardized, re-usable and scalable data research networks to create a self-sustaining economic model for re-using EHR data for research purposes, such as determining protocol feasibility and matching patients to appropriate trials. (In contrast, a similar US effort, the PCORnet project of the Patient Centered Outcome Research Institute (PCORI) will cobble together in a one-off fashion 11 clinical data research networks to support observational studies, a model that will lead to data that can't be shared and a network that will always rely on government funding.)

Individual member states of the European Union are also undertaking significant initiatives to accelerate biomedical research. For instance, the Clinical Practice Research Datalink (CPRD) is a UK National Health Service (NHS) offering that provides: de-identified clinical data from some 45 million patient records for data-driven research; a large primary care database for observational studies; and a research network of primary care and other practices that can be utilized for interventional (clinical trials) research.

Today, the U.S. lags considerably in pursuing such bold initiatives. Instead, our health care facilities are compartmentalized and non-interoperable, and our public research apparatus is almost entirely divorced from private-sector capabilities, which leads, inevitably, to constant "reinvention of the wheel."

Several of those appearing before the Committee have endorsed the concept of developing "research networks." We agree with the concept but have some questions about its execution. Certainly, new data research networks could be helpful in conducting outcomes research – areas like comparative effectiveness and drug safety. These studies rely on analysis of data, including "big data." We are skeptical, however, that new research networks cobbled together with government funding will be particularly useful for the conduct of the pivotal clinical trials that lead to the approval of new drugs and treatments. Efficient management of large, multi-site clinical trials requires in-depth knowledge of which investigative sites can recruit the requisite number of patients, follow protocols, and provide reliable data for regulatory review. Today, high-quality, functioning clinical research networks are maintained by leading global CROs and we question the wisdom, as well as the utility, of committing government funding to the creation of new silos of academic research networks to conduct large-scale clinical trial programs.

What Congress Can Do

To provide an example of a step that would break down research barriers, we believe there is an opportunity to **engage private-sector expertise to complement the scientific expertise housed within the NIH, especially for new initiatives like the National Center for Advancing Translational Sciences (NCATS).** The CRO industry possesses project management, data management, patient recruitment and feasibility expertise that simply does not exist within the NIH or among academic researchers. Congressional direction for NCATS to work more closely with industry would, we believe, accelerate this translational research.

Global Tax Competitiveness

With member companies that conduct research around the world, we would suggest specifically that Congress look first at the impact of current U.S. tax policy on the research and development enterprise. With corporate tax rates among the highest in the world and having made little progress toward an equitable system for taxing foreign earnings, the U.S. is increasingly disadvantaged, even in comparison to what may be considered high-tax countries. While there are many reasons to conduct clinical trials on a global basis, including access to populations and markets, U.S. tax policy currently encourages clinical trials to be placed outside the country.

What Congress Can Do

Although it was enacted in 1981, the current R&D tax credit is an "extender" which requires re-enactment each year and so cannot be relied upon by the companies that are making R&D

investments. A related issue is that the R&D credit currently is focused only on the owner of the technology, not on the company that actually does the development work and employs research staff, and so may not incentivize U.S. hiring most fully. These two factors make the U.S. increasingly uncompetitive in relation to other countries, such as the UK, France, Austria and Canada when it comes to the hiring of clinical research staff and the placement of clinical trials. ACRO urges the Committee to work with your colleagues on the Ways and Ways Committee to make the R&D tax credit permanent and to adjust the current limitations on allowing the credit to 'flow through' to the companies that actually perform development work, instead of stopping at the technology owner.

Current U.S. tax law prohibits the R&D credit for "contract research" and further limits to 65 percent the amount of the credit the research sponsor may take when using contract research providers. Increasingly, CROs are making the decisions about where clinical trials are being placed and ACRO members now employ more development staff than the pharmaceutical industry. The employment has shifted along with the research dynamic but tax law has not kept pace. The result is CROs have an incentive to conduct clinical trials in other countries because they cannot avail themselves of the R&D tax credit within the U.S. **Our solution is to simply make the 35 percent of the tax credit that currently evaporates when research is contracted out available to companies performing contract research.** We believe this is a simple and inexpensive policy change that would help keep research jobs and innovation within our borders.

<u>Electronic Health Records (EHRs) and the Discovery/Development/Delivery Cycle</u>

With rapidly increasing adoption of EHRs across hospitals, doctors' offices and other delivery sites and a multi-billion dollar investment by the U.S. government in the "meaningful use" (MU) of such systems, there is no doubt that "big data" (which includes clinical care records, research data, patient-generated and wearable device data, and a range of other data sources) has significant potential to enhance patient safety, improve healthcare, and advance medical science. Within the *development/delivery* cycle, access to EHR data is essential for comparative effectiveness, observational and outcomes studies; and in the conduct of clinical trials EHR data has the potential to facilitate improved protocol design, patient identification and recruitment, adverse event reporting, and the like and thereby shorten the time and cost necessary to accomplish safety and efficacy testing for new biomedical products.

Based on a public opinion poll co-sponsored by ACRO and conducted in May 2013 by Research!America, 53 percent of people hear about clinical trials through the internet or online sources but only 24 percent hear about them from their doctor. Further, only 6 percent of those surveyed said their doctor has ever recommended they participate in a

clinical trial. Yet, 60 percent said a doctor would be their preferred source of information and 72 percent said they would be somewhat or very likely to participate in a clinical trial if recommended by their doctor. By far the easiest way to facilitate this important doctor-patient interaction would be through an EHR system that contains information about relevant clinical trials.

But significant barriers to EHR use, including complicated Informed Consent requirements and concerns about the privacy and confidentiality of individuals, and the lack of a consistent regulatory framework for "secondary use" of health data, have made for very slow progress in the utilization of data to accelerate the discovery/development/delivery loop. Instead, we see isolated experiments in data sharing and re-use, with a preponderance of non-interoperable, purpose-built one-offs, like the FDA's Sentinel Initiative research network.

Information-based research is key to the medical advances that are urgently needed by patients, and central to achieving a transition to an evidence-based, value-driven healthcare system. What is needed is a policy framework that encourages EHR interoperability and data re-use, coupled with regulatory mechanisms that effectively protect (and enforce) data security. We also need to provide incentives for data sharing and fluidity, and a sustainable business model for using EHR data for discovery/development/delivery purposes.

<u>What Congress Can Do</u>

Today a number of agencies and offices – including the Office of the National Coordinator for Health IT (ONC), the FDA, NIH, CMS, HHS's Office for Civil Rights (OCR), the Federal Trade Commission (FTC), the Federal Communications Commission (FCC) and even the National Institute of Standards and Technologies (NIST) – are engaged in developing policies to address various aspects of the "big data" space, from EHR data to telehealth, wearable devices to mobile applications. Because the use and re-use of health and related data is key to accelerating the discovery/development/delivery cycle, we urge the Committee to include testimony from agency and other stakeholders on the topic of "big data" in a future Roundtable.

Two specific recommendations ACRO offers for the Committee's consideration are:

- Congress should encourage **inclusion of new EHR functionalities that will facilitate clinical and data-driven research** as part of ONC/CMS (Office of the National Coordinator/Centers for Medicare and Medicaid Services) **Meaningful Use Phase 3 requirements.** We envision a scenario where EHRs are integrated with clinical trial data from clinicaltrials.gov and can match eligible patients to appropriate research protocols. The EHR would incorporate a "pop up" box to inform the physician of the

availability of a potential clinical trial for their patient. This would greatly speed the recruitment process, reduce development time and cost, and bring treatments to patients more quickly. This may require some small additional appropriation for the National Library of Medicine, which administers clinicaltrials.gov, but we believe this is a small price to pay for the potential billions of dollars in savings in R&D costs, not to mention the added patient benefits.

- Congress should **amend HIPAA to define <u>data research</u> as part of *health care operations* at § 164.506** in order to allow the use of protected health information (PHI) for non-interventional studies, in the same manner that PHI may be used today for quality assessment and improvement activities, outcomes evaluation, and the like.

<u>Driving Innovation at the FDA</u>

One of the questions in the Energy and Commerce Committee's initial white paper on the 21st Century Cures initiative was what the NIH and the FDA have learned from partnerships like the Biomarkers Consortium, the Critical Path (C-Path) Institute, and the Clinical Trials Transformation Initiative (CTTI). As we did in testimony to an FDA Public Hearing on "Modernizing the Regulation of Clinical Trials" in 2012, ACRO is pleased to provide the Committee with a perspective on that question.

In March 2004 the FDA published the report titled, "Challenge and Opportunity on the Critical Path to New Medical Products." The white paper posited the need for "new tools to get fundamentally better answers about how the safety and effectiveness of new products can be demonstrated, in faster time frames, with more certainty, and at lower costs." The report called for a joint effort by industry, academia and the FDA to identify key problems and develop targeted solutions along the "critical path," noting that most of the recent cost increases in the process of getting to new medical products are in the *development* phase – from pre-clinical discovery work through the end of human clinical trial testing, between discovery and launch, in other words.

To advance the Critical Path Initiative, the FDA has supported and continues to support, either financially (to the tune of several million dollars each year) or with personnel or both, a number of public-private collaborations, including the Critical Path (C-Path) Institute, the Clinical Data Interchange Standards Consortium (CDISC) and the Clinical Trials Transformation Initiative (CTTI) and there has been some real progress in development of the "tool box" that supports the biomedical product development paradigm.

For instance, CDISC has more than a dozen data standards and innovations developed, tested and rolled out for use, and C-Path has submitted to the FDA for review more than 60 potential biomarkers, disease models and patient-reported outcomes. Similarly, the NIH Biomarkers Consortium, in which several of our member companies participate, has undertaken data sharing and data mining projects; one project, for instance, analyzed aggregated placebo data from large, industry-funded trials to determine whether the protein adiponectin is useful as a predictive biomarker of glycemic control.

But actual product development remains costly, slow and unproductive. As was true in 2004, it still takes over a billion dollars across a timeline that can take up to 15 years to bring a new biomedical product to market. In fact, many of the themes, if not the specific recommendations, made in the 2004 FDA Critical Path white paper were repeated in the 2012 PCAST report. So we must ask, how much progress have we actually made? And what is standing in our way?

Unfortunately, in assessing the output of agency-funded collaboratives we see very little in the way of projects that might qualify as aiming to 'transform' the *development* paradigm. Instead, we see "research on research" – with surveys, white papers and other publications, recommendations, meetings and educational initiatives, and the like; all of which, we believe, is unlikely to facilitate significant change to current practices, let alone transformation of the enterprise. Simply, understanding that certain practices are wasteful or ill-advised will not, on its own, change those practices.

To illustrate by example: as long as Federal or industry research grants flow to institutions where completion of IRB review averages over two years, without any negative consequences, you can expect that the timeline for IRB review at those institutions will not improve more than marginally. To change behavior the FDA, and the NIH must *expect* the use of central IRBs, not simply endorse their use.

<u>What Congress Can Do</u>

We are optimistic that the early success of the new Breakthrough Therapy designation that was part of FDASIA will have broader implications for drug development. With 156 requests made to the FDA for this designation, and 44 approved, in just over two years there was clearly pent up demand among medical product developers. While by nearly all accounts this program has been successfully implemented by the FDA, we note that it took a specific Congressional directive for the agency to embrace this innovative new pathway.

Time and again ACRO member companies see innovative approaches to clinical trials – which had the blessing of senior FDA officials – derailed by risk-averse auditors in the field. There

must be an innovation culture throughout the FDA to truly drive change in the development process. Our concern remains that in the absence of specific legislative direction and authority, FDA will be hesitant to pursue new innovative ideas that reduce the development time and cost for all new therapies and treatments.

ACRO suggests two actions that would help to re-focus the FDA Critical Path Initiative:

1. **Engage the GAO or other 3rd party to review and prepare a report answering questions such as** – Is the FDA, an agency with scarce resources, receiving an adequate return on its investment in these initiatives? Are these public-private endeavors meeting their objective to produce truly "transformational" outcomes? Might a more collaborative approach with industry produce superior results, at less cost, while the agency can use the funds from these initiatives to, for instance, increase its review staff or invest further in regulatory science?

2. **Direct that the FDA appoint a Chief Innovation Officer** who shall be responsible for overseeing the Critical Path Initiative and will have the authority to agree to and enforce new, innovative approaches to drug development.

In Conclusion

Today CROs employ more scientists and research personnel in *development* than do the pharmaceutical and biotech companies that typically initiate the process of *discovery.* And we are increasingly involved in the application of data analytics to the outcomes, safety, comparative effectiveness, and other data derived from the *delivery* of (and payment for) health care.

In the clinical trial process, CROs operate in the nexus between research sponsors and regulators. So, we have a unique appreciation for the many competing interests that must be balanced in the conduct of clinical research – speed, cost, efficiency, innovation, transparency and, most importantly, patient safety.

A full 10 years since the publication of the FDA *Critical Path* white paper, we have reached a stage where bold action, leadership and accountability are required to move the drug development enterprise forward so that we all can benefit from new therapies and treatments sooner. To do less is to remain stuck in a product development model that is too costly, too long and simply does not produce the number of new products needed. The task at hand is both large and enormously important, and ACRO is fully prepared to respond to the Committee's Call to Action to create a scientific, regulatory, business and policy environment that will indeed lead to 21st Century Cures.

ACRO thanks the Committee for the opportunity to provide this comment and we look forward to continued dialogue. Please do not hesitate to contact us for further information at any time.

Respectfully,

Douglas J. Peddicord, Ph.D.
Executive Director