

interview

Steve Carney talks to Doctors Califf, Kramer and Behrman on the Clinical Trials Transformation Initiative

The Critical Path Initiative is the US Food and Drug Administration's national strategy for modernising the sciences through which FDA-regulated products are developed, evaluated, manufactured, and used. The Initiative was launched in March 2004 to address the steep decline in the number of innovative medical products submitted for approval, despite the enormous breakthroughs being made in biomedical science. Although initially conceived as a drive to apply discoveries in emerging areas of science and technology to medical product development, the Initiative has since expanded its scope to include all FDA-regulated products.

Steve Carney (SC): *Could somebody give a potted history and an overview of the Critical Path Initiative?*

Rachel Behrman (RB): I can start with that one. The Critical Path Initiative, which the FDA launched a little over four years ago, is a concerted effort to modernise the tools necessary for developing, evaluating, manufacturing and using FDA-regulated products. So it's a concerted modernisation and innovation initiative.

SC: *We've heard quite a bit recently, especially on the Internet, about the Clinical Trials Transformation Initiative (CTTI); could somebody explain to me the reasons behind why that was established?*

Robert Califf (RC): I can take that one and get the discussion started. Like many cooperative efforts, there are probably a lot of reasons why people would want to join it; but I think the main reason that we were interested in joining with the FDA, is that there is a great degree of frustration about the inefficiency of

doing clinical trials today. We're increasingly, inappropriately hearing from many sectors of society, that we need better evidence upon which to base decision-making, whether it's what should go on the formulary, or what drugs or devices an individual person should be exposed to in practice. Yet, our system for generating evidence is beleaguered, expensive, inefficient and difficult to manoeuvre. The end result of all this, of course, is that we have great difficulty producing the evidence that we need to guide decision-making about drug development or device development, but also for use in practice. We often have to make prescribing decisions with inadequate information, because we just don't have it. We were highly motivated and many of us have been working together for years trying to get trials done and despite all our best efforts watching things become more difficult and more inefficient. So the hope was that by forming a partnership and working together we could begin to improve our ability to provide society with what it needs.



Robert M. Califf, MD

Judith M. Kramer, MD, MS

Rachel E. Behrman

See box on the following page for biographies

RB: Could I expand on that from the FDA perspective? What we've learned through the Critical Path Initiative and the cornerstone of the Critical Path Initiative, is partnership; that for an enterprise such as the Clinical Trials Enterprise, there are systems problems that can't be solved by any one entity, but by bringing everyone to the table we have a much better chance at addressing the critical problems that Rob has mentioned. Finally, in terms of medical product development and use, if we can't get them into the clinic and,

as Rob was saying, evaluated, so that we know how and when to use them and the safest, most effective way to use them, then really the whole discovery process doesn't make much sense anymore, because we are, in fact, developing and producing the products that bring the advances to America and the world, that are needed.

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SC: *You've partly answered my next question, but I'll combine it with another one; what is the CTTI trying to accomplish and how will you assess success?*

RC: I think Judy should describe some of the specific programmes that we have just started, because it would give people a good idea of what we're actually, concretely, trying to accomplish.

Julie Kramer (JK): I think Robert is referring to the fact that we expect to accomplish our

goal through actually doing projects that will provide evidence of ways that we can improve the conduct of clinical trials. So one example, the initial project we started, is a project to look at the way we monitor clinical trials to assess the quality of the data, in terms of whether it really is reliably answering the question that we're asking. We know that monitoring can take up to two thirds of the resources of a clinical trial. If we can somehow assure that we maintain quality, but make that process more efficient, obviously it can have a tremendous impact on the number of trials we can conduct, because it would take fewer resources to conduct any one trial. Rob, were you thinking in terms of the projects as a measure of success when you were asked the question of how we assess our success? Are you thinking in terms of the projects themselves and the results of the projects influencing how we conduct trials being a measure of success?

RC: I would say, our method is to launch specific projects with specific deliverables which, as Rachel said, would be evidence about how to do trials better. We will not have control over what

actually is done, because that will be up to the people who are doing clinical trials and we're obviously in this public-private partnership not writing regulations that dictate what will be done; but we've seen many examples where we can provide the evidence about best practice, such that those who write regulations and those who conduct research, will do it better.

JK: I think one comment I would make about that, is that we're hoping that through the broad representation that we have in the member organisations for CTTI, that the participation of all sectors will increase the chances that the results that we find in these projects will be adopted broadly; and the member organisations are already talking about ways that they can influence the dissemination of the findings and promote adoption of practices once we have the evidence about better ways to do trials.

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Robert M. Califf, MD

Dr. Califf graduated from Duke University, in 1973 and from Duke University Medical School in 1978. He performed his internship and residency at the University of California at San Francisco and his fellowship in cardiology at Duke University. He is board-certified in internal medicine (1984) and cardiology (1986) and is a Master of the American College of Cardiology (2006).

He is currently Vice Chancellor for Clinical Research, Director of the Duke Translational Medicine Institute (DTMI), and Professor of Medicine in the Division of Cardiology at the Duke University Medical Center in Durham, North Carolina. For 10 years he was the founding Director of the Duke Clinical Research Institute (DCRI), the premier academic research organization in the world. He was recently acknowledged as one of the 10 most cited authors in the field of medicine by the Institute for Scientific Information (ISI).

Dr. Califf has served on the Cardiorenal Advisory Panel of the U.S. Food and Drug Administration (FDA) and the Pharmaceutical Roundtable of the Institute of Medicine (IOM). He was the founding director of the coordinating center for the Centers for Education & Research on Therapeutics™ (CERTs), a public/private partnership among the Agency for Healthcare Research and Quality, the FDA, academia, the medical-products industry, and consumer groups. This partnership focuses on research and education that will advance the best use of medical products. He is now the co-chairman of the Clinical Trials Transformation Initiative (CTTI), a public/private partnership focused on improving the clinical trials system.

Judith M. Kramer, MD, MS

Dr. Kramer is Executive Director, Clinical Trials Transformation Initiative (CTTI), and Associate Professor of Medicine at Duke University Medical Center. She is also co-investigator in the Duke Center for Education and Research on Therapeutics (CERTs) focused on cardiovascular

disease and member of FDA's Drug Safety and Risk Management Advisory Committee. Over her career, Dr. Kramer has practiced clinical pharmacy, general internal medicine in a rural community, and clinical research, both pre-approval and post-approval. Her clinical research experience has included working in the pharmaceutical industry (Burroughs Wellcome Co-VP Medical/ GlaxoWellcome-International Director, Cardiovascular/Critical Care) and Duke Clinical Research Institute (9 years as Chief Medical Officer and previous Principal Investigator, Duke CERTs). From 1999-2001, Dr. Kramer was Founding Director, Masters Program in Clinical Research at Campbell University in NC. Dr. Kramer's research interests include finding safe and effective cardiovascular therapies, assuring persistent use of life-saving medications, and evaluating new methods to study post-marketing safety of drugs and devices.

Rachel E. Behrman

Rachel E. Behrman is the Associate Commissioner for Clinical Programs and Director of the Office of Critical Path Programs, U.S. Food and Drug Administration. In that capacity, she is responsible for developing, coordinating, and implementing policy and scientific programs aimed at innovating development and regulation of FDA-regulated products. Dr. Behrman joined the FDA in 1989 and has held a number of positions in the Center for Drug Evaluation and Research, including medical reviewer and team leader in the Division of Antiviral Drug Products and deputy director of the Office of Medical Policy. Dr. Behrman is a board certified internist and infectious disease subspecialist and a Fellow of the American College of Physicians. She received her A.B in mathematics from Washington University, her M.D. from Mt. Sinai School of Medicine, and her M.P.H. from The Johns Hopkins School of Hygiene and Public Health. She lives in Bethesda, Maryland, with her husband and their four children.

RB: If I can add to that and emphasise a point. We're picking projects; we have a very ambitious agenda ahead of us, obviously. We're starting with projects that are timely, there are things that we've been recognising for several years, which need to be addressed that have very concrete deliverables as Rob mentioned, within a reasonable time frame, so that it will be easy for us, in that respect, to gauge whether we are on track; whether the system that Judy is mentioning of getting everyone to the table, engaged and committed to trying to implement these changes and to determine whether that system is, in fact, working.

RC: I would say, in the broadest perspective, success would be that we're able to do clinical trials more quickly, get results that are more accurate and that build confidence in the public and those developing medical products, that we know the balance of risk and benefit with more precision at the time these products get on the market and as they're being used. That's a goal which is subject to many forces, other than CTTI. The best we can do is, through these specific projects, lay out how to do it better with all these different stakeholders having input.

SC: *Perhaps, unfortunately, you've been compared with the "A-team" in some reports and I quote now "if it [the CTTI A-team] can't come up with evidence and ideas for reconsidering the rules for clinical trials, it can't be done." Do you think this is placing undue pressure upon the team to be successful in this and how do you think you will cope with such pressure?*

RC: Pressure is good. What's wrong with being the A-team? I'd much rather be the A-team than the B-team. Because maybe Dr Kramer is the one who is feeling the most pressure—since she is the CEO—she should respond to that.

JK: I'm used to working with Rob and I agree with him that pressure is good. What's worse than having pressure on us is doing nothing. I think Rob outlined it perfectly at the beginning; we're all so frustrated that the number of questions that we have to answer is increasing and our ability to provide the evidence to answer those questions seems to be decreasing in terms of timeliness and scope of questions we can address. We'll take the pressure. I actually believe that this initiative really does have a better chance than any initiative that is taken on by a single sector; traditionally there have not been initiatives as broadly representative as this. I'm hopeful that this characteristic will help us to be successful.

RC: The motivation for me is that there is

much greater pressure than what you describe in terms of outsiders looking in. I still get to practise as a doctor. When I have to prescribe a medication or recommend that a patient get a device and I don't really know the balance of risk and benefit, because we haven't done the research, that's all the pressure I need. We have a long way to go to generate the information that we really need to make the best decisions.

I actually believe that this Initiative really does have a better chance than any initiative that is taken on by a single sector

SC: *You mentioned then, that you thought that this initiative was different from traditional approaches. Do you think you could outline how you think CTTI is different from other efforts in the past and how you think those differences will help to improve clinical trials?*

RB: I can start. The other efforts in the past have not been, as Judy mentioned, as inclusive and they certainly haven't had the broad public-private feel or flavour to it, or a flavour of broad participation of the US Federal Government, as well as others such as observers from the EU and obviously the various sectors within the development community in the US.

RC: I would say (I'm still saying this on other projects that I'm involved in) that you may have the academics off in one corner doing their thing and then you've got industry in another corner worried about regulatory things. The FDA may be dealing with both in different venues and CROs with a different perspective from academic research organisations or pharmaceutical device companies. In this case, we've brought them all together under one big tent. Like many other things in life today, this can lead to complicated interactions, but it's really the only hope of having a systematic approach to generating evidence. I might add it's a big deal today in the US, because it's a clearly stated goal of the new administration to up-fit the infrastructure for evidence-generation in the United States, so that we can assure our own citizens that they're getting the right treatment at the right time.

This will create better knowledge that could lead to the development of better products

SC: *Do you think that, should CTTI be successful—which we all hope it will be—that it will result in an increase in drug approvals in the future, maybe address the productivity*

gap that we hear an awful lot about? If so, what do you think the timeframe for this is likely to be?

RB: That's precisely the reason behind CTTI and other efforts within the Critical Path Initiative. It's hard to say that a specific number of approvals will increase by a specific per cent, but the whole notion is that the medical practice development paradigm within the United States and in the world is a little bit broken. There's no question that if we succeed until the NEC says we're confident that we will, that we will see more products coming to market, we will see them coming to market more efficiently. That will free up resources to devote to answering other questions and the whole process will then become more efficient and more productive and better at answering the necessary questions.

RC: I agree that this, of course, is the hope and assuming that the quality of discovery of medical products was constant, if we get more efficient and more effective at doing clinical trials, of course we will have faster time lines to approval. It's also possible that if we can do more research at a lower cost with higher quality, that this will create better knowledge that could lead to the development of better products.

SC: *Do you think that pharmaceutical organisations that participate in this will be viewed more favourably by the public?*

JK: I think that it's fair to say there's been a lot of scapegoating going around in terms of where the problems are, when we've run into trouble with, whether it be drug safety or how fast we develop new innovations and treatments for diseases with an adequate treatment. I think the pharmaceutical industry has been the recipient of some of the blame, very frequently. We find that in this kind of initiative, where we're putting together people who are focused on improving research and development, all sectors present are really committed to the goals that we set. As we work across sectors with everyone at the table, to the extent that people truly commit themselves to what we're trying to do and are honest and forthright in their dealings, it will improve the respect for all sectors from all other sectors. Committing to a common goal, which serves the public and the patients who need these treatments, has to be something that will be a positive activity for all members, including the pharmaceutical, device and biologics industries. So I hope it will improve that public image. We certainly have found enthusiasm and sincere support for the

underlying purpose that we're operating under and very hopeful about that in the future.

SC: Following on from that, what organisations are currently part of CTTI?

JK: Following on from the conversation we've had, we have a very broad representation of organisations, a very diverse membership that includes industry, pharmaceutical companies, biologics companies, device companies and clinical research organisations. It also includes academic institutions and professional societies; we have representatives from three FDA centres; we have the Center for Drugs, the Center for Biological Evaluation and Research, the Center for Devices and Radiological Health and someone from the Good Clinical Practices Division. We have clinical investigator groups— independent clinical investigator groups, that aren't associated with academic institutions. We have trade organisations: the Pharmaceutical Research and Manufacturers Association; BIO and the Association of Clinical Research Professionals. We actually have a regulatory law firm. We even have a private equity firm that's interested in sharing their perspective, in terms of what's worth developing and good ways of doing that, what kind of evidence is important to them as funders. We're in the process of identifying international regulatory agencies, patient advocacy groups and an at-large member that will provide a perspective that's not present among all the member organisations that I listed. We have close to 50 member organisations, very broadly spread across the sectors that I mentioned. We're very encouraged about the broad participation going forward.

RC: I would add that I think this very broad representation is critical and to your question of confidence in the pharmaceutical industry—it's my belief that high-quality, transparently derived information that is communicated effectively is the case. To the extent that what CTTI does is to identify practices that lead to that result from clinical trials, it will have a boosting effect on confidence, which is obviously sorely needed.

JK: It's not just confidence in the pharmaceutical industry; it is confidence in the entire enterprise. So it's confidence in those of us who regulate it. It is confidence in the investigators that execute the trials. It is confidence in those that are responsible for the human subject protection functions of the trials. It's the entire enterprise that has lost a certain amount of public trust and efforts such as this can help restore that.

SC: Maybe I could ask how do you select projects for this initiative; what criteria underpin the acceptance of a project for inclusion in the trials initiative?

JK: First of all, we've put out a principle that any individual or organisation, who is interested in submitting a project idea or project concept, may do that. The Executive Committee developed and established the scope for our projects and the criteria for selection and these are available on our public web site for anyone to look over in detail, that's at www.trialstransformation.org. The project concept, any project concept that is submitted within the scope as stated on our web site, will be considered. It will be circulated to every Executive Committee and Steering Committee member, although the Steering Committee has set up a sub-Committee of about 10 individuals to review these project concepts in detail and decide which ones will be developed further into a detailed project plan. Ultimately, the recommendation as to whether we should conduct a project that has been laid out in the detail plan, the recommendation is made by the broad Steering Committee on the recommendation of this sub-Committee and then the Executive Committee makes the final decision and we go forward. I think it's probably better for individuals to look at the detailed criteria on the web site, than for me to read them to you at this point.

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SC: Do you separate out the trials by therapeutic area, because obviously a trial design is going to be radically different depending upon the therapeutic area?

JK: I'll take the first stab at that. We're looking for solutions that really have broad applicability to the conduct of clinical trials, regardless of what therapeutic area we're dealing with. That's because we're not dealing with the specific design issues required for regulatory approval and therapeutic areas. The fundamental way we conduct trials stays really applicable across therapeutic areas. Rob, do you have any comments on it?

RC: I think you said it well. There are principles of human studies that involve ethics and also methods of conducting the trials that really should cut across any sort of investigation. In fact, many of us would argue that problems

have arisen because different areas of clinical investigation have considered themselves more different than they really are. After all, in every case we're talking about taking a human subject, getting concerned in interventional trials, doing an intervention based on some assignment scheme and then collecting data that informs us. I think we're finding that across the array of devices, drugs, even behavioural interventions, there are commonalities that have sort of gotten lost in the woods; when you step back and take a broader view, we could simplify and get better answers with better protection of human subjects, at a lower cost. **RB:** I certainly think the first products that we've chosen speak to that. They are very cross-cutting and they do not impact one medical product sector any more than another one.

SC: What resources will be available to support these projects?

JK: I'll answer this one, since I'm responsible for overseeing the whole portfolio of projects. We expect to conduct the projects with multi-disciplinary project teams, [representing] the broad representation of our members. We expect that these teams will be staffed primarily through incoming contributions of personnel, from member organisations and other volunteers. In addition, there are some things that will require actual dollar funding and we've established a project fund that accepts voluntary contributions from any individual or organisation that is interested in supporting this effort. There will be Executive Committee oversight of the distribution of these funds.

RC: I would add to that, we're just entering a new administration in the US and the focus of CTTI, because it is an FDA academic public-private partnership in the US, is the difficulty that we're having in the US getting trials done. We always have agreed that we'll keep an eye on the international issues, because we need harmonisation for many reasons, but I have great hopes that more money going into the US system at all levels of generating evidence, is going to make the job of CTTI easier. In other words, if health systems in the US are better equipped with electronic records, we may find that we can speed up enrolment quite a bit and get access to data that would not require that we do it the old fashioned way, which is very labour-intensive.

SC: I'm assuming that there's going to be some standardisation for clinical trial data, set up across data base standards?

RC: Some of us are really excited today, because the House [of Representatives] just passed a Bill

yesterday that would put \$20 billion into health IT in the United States. We're not just talking about standardisation for clinical trials. Much of the money would go for standardisation for clinical practice, which would really make clinical trials much easier to do.

SC: *Finally, how do you think the projects will lead to improvements in the clinical research enterprise?*

RB: I'll start with that. I'd like to talk a little bit about how this will lead to improvements in the health of our citizens; and that is, very simply, that the better the information, the more information we have about how to use these medical products, the more medical products we have available, the healthier lives we will all lead. There's no question that if we're wasting resources, we're not then appropriately protecting the public in terms of generating the information and the evidence we need, nor are we protecting those involved in the trials, because we're wasting time and effort on other, if you will, distractions. We think the projects will lead to concrete improvements in very specific aspects of clinical trial conduct and that, in turn, will translate into better information, more information and more availability of safer products.

RC: I think almost anyone can understand that right now in the United States, it takes over six months to really get a trial started after

the protocol has been agreed upon and sent out to the clinical sites. If that were cut in half, obviously just that alone, there would be no change in anything except that we would get the answers more quickly, which would be very good for the public and very good for health care systems.

We think the projects will lead to concrete improvements in very specific aspects of clinical trial conduct and that, in turn, will translate into better information, more information and more availability of safer products.

SC: *How would you see the information from these trials being disseminated, especially as this is a public/private partnership and the public seem to be keen to see the outputs of some clinical trials; is there any provision for publishing or making the trial information available to the general public?*

JK: Absolutely. One of our fundamental tenets is that this will be publicly available. We are actually (I think today) putting the detailed project plan for the monitoring projects that I mentioned, up on our web site; so we're not even expecting to wait until the end of the process, but want the public to be aware of what we're doing as we're doing it. The Steering

Committee at our last meeting in December (2008) has already started talking about the best ways for them to disseminate information on the results of our trials. So we realise that the evidence we generate about how we can do clinical trials better and improve the quality of the output, has to be disseminated broadly and be available to all the people making decisions about how they're going to conduct their research.

RB: Finally, the point is that good quality research and information coming out of CTTI may very well affect the FDA in terms of how we officially think and speak, as does any source of good quality information, when we think about necessary guidance and regulation.

JK: I'd like to say that we hope to use, we certainly will use, our web site among other opportunities to disseminate this information, so that's a good place for people to keep an eye on what's happening.

SC: *Thank you very much to everybody. It's been very interesting for me and I hope it's been interesting for our listeners as well. I wish you all the luck in the world for getting this thing off the ground and I hope it really does results in a huge improvement in clinical trial design that everybody will benefit from in the long term. So thank you very much indeed*

Participants: Thank you and take care.