Statement of

Robert J. Meyer, MD[1]

Director of the Virginia Center for Translational and Regulatory Sciences

Associate Professor of Public Health Sciences,

University of Virginia, School of Medicine

Charlottesville, Virginia

Before the House of Representatives

Subcommittee on Health, of the

Committee on Energy and Commerce

Hearing: 21st Century Cures: Modernizing Clinical Trials

July 9th, 2014

[1]Note: Dr. Meyer is participating in this hearing per invitation and on his own behalf; the views expressed in this statement are not necessarily those of the University of Virginia or of the Commonwealth of Virginia

Chairman Pitts, Ranking Member Pallone and Members of the Committee. I am Dr. Bob Meyer, Director of the Virginia Center for Translational and Regulatory Sciences at the University of Virginia, School of Medicine, where I also serve as an Associate Professor of Public Health Sciences. I am a pulmonary physician by training who, previous to my move to Virginia, has held senior leadership positions within the Center for Drug Evaluation and Research at FDA, as well as at Merck & Co., Inc. At Merck Research Labs, I was head of Global Regulatory Strategy, Policy and Drug Safety and therefore was a key participant in their Late Stage Development Committee, the committee responsible for oversight of the planning and conduct of clinical trials in support of Merck's portfolio of new medicines and vaccines. I am very cognizant of the challenges of clinical trials both from a regulatory and industry perspective. Therefore, I am pleased to be here today to share my perspective on the topic of modernizing clinical trials, as this is an important and integral part of the broader considerations on providing for a robust therapeutic development ecosystem in the United States, one that both provides for US patients having access to important new, effective medical advances, as well as a healthy biotechnology industrial sector that assures employment to a large, sophisticated workforce.

It is well documented that one of the major categories of expenditure in developing a new therapeutic is the expense of conducting the necessary late-stage (or phase 3) clinical trials, which are intended to address the regulatory expectations in the US and beyond. Modern clinical development programs are generally large, complex and often global in both scope and conduct. As a result, these programs are increasingly expensive. In fact, the proportion of total clinical development expenditure that is devoted to phase 3 trials alone is roughly 75-95% of the total spend, depending on the disease category.[i] Compounding this is the fact that the success rate for drugs entering into phase 3 in achieving final approval is falling, with the rate now approximating 50%. This means that not only is the conduct of phase 3 trials for a new drug a large investment, but these expenditures are sometimes for naught. This adds to the phase 3 clinical trials expenditures per successful drug.

There are a number of drivers that have contributed to the growth in larger, longer and more complex phase 3 clinical trials, including regulatory demands. However, I think it important to not solely focus on this issue as being a consequence of regulatory requirements, as these drivers are multidimensional.

Let me make an important point first and foremost - some have proposed that one means of addressing both the costs and failures of phase 3 trials is to shift regulatory decision making earlier, leaving "confirmatory" efforts to the post-approval setting. I would caution against this. The fact that many products fail in phase 3 reflects the realities of science as much as any issue correctable in the design and conduct of trials. Indeed, since roughly half of phase 3 failures can be ascribed to failures in proving effectiveness[ii], this signals a clear cautionary note for lessening the demands during phase 3. Additionally, these proposals often cite the desire to use real world data to finally confirm effectiveness. I do not believe that current observational methods allow for the kind of rigorous assessment of efficacy that patients and their physicians deserve and payers demand, even given the very real promise of big data and the systematic research use of electronic health records.

What then are some of the considerations that I would recommend be taken into account in the discussion of how to effectively modernize clinical trials?

1. The first considerations relate to opportunities in standardization. In phase 3 programs, there is a large amount of time expended getting from study concept to first patient enrolled. The effort and time spent by sponsors in all aspects of study start-up are considerable (time from trial concept to final protocol, to then identifying study sites capable of rigorously conducting the research while providing for a sufficient patient-base, and then in the mechanics of training the study site in the particulars of the study and getting the requisite Ethics Committee approval). All this is effort occurs prior to even one patient being enrolled. And sponsors go through this time and

again, as de novo efforts, for each program. These efforts represent systemic inefficiencies which in turn raise two important points worthy of consideration.

a. The first is the enhanced development of effective, durable clinical trials networks that have the potential to obviate the need for approaching each new trial as a de novo effort. Networks can have identified patient populations, clinic sites and ongoing research efforts that would help reduce time and efforts spent in study start up. There are efforts towards clinical trials network development in certain disease areas (a good example is the 2014 initiative from the National Cancer Institute in its National Cancer Trials Network, undertaken in response to the Institute of Medicine's call for such a network to reinvigorate innovation in cancer therapeutics).[iii] However, while there are instances of successes in trials network development, this model is not as wide spread as it could or arguably should be, particularly taking into account the varied areas of unmet medical needs (e.g., pediatric drug development). While one might regard Contract Research Organizations (or CRO's) as perhaps being tantamount to trial networks given their focus on operational efficiencies, the competitive nature of the many clients they serve is an impediment to the CRO's achieving anything close to the kind of efficiencies possible in networks. The issue of competition means that the broader development of clinical trials networks would likely not come from industry or CROs alone, but would entail Public-Private partnerships, with the appropriate agencies of the federal government partnering with industry and academia in a dedicated effort to set them up and maintain and hone them over time.
b. A second concept that is not at all exclusive of the idea of broader trial networks is that of the development of master protocols. Such master protocols could serve as the basis for use by different investigators or sponsors with minimal modification (save for the details of the particular test product). When faced with important diseases being targeted by

multiple sponsors simultaneously, each interested in developing new therapeutics for those diseases, there could be a significant opportunity for developing such master protocols. For instance, clinical trials for the treatments of melanoma – a deadly form of skin cancer – are burgeoning right now. But the trials differ in details of design which leads to inefficiencies for the sponsors, the sites and in potential patient recruitment. The benefits of having well-honed standardized protocols to inform the protocols for trials undertaken within a targeted disease area (particularly where networks have been developed) could certainly enhance the efficiencies in the planning and conduct of these trials. Use of master protocols could also enhance the ability to interpret these trials in cross-study comparisons to assess relative efficacy, safety or other attributes considered important to physicians, patients and payers, since the patient populations and endpoints would be highly similar. As with networks, however, this again entails broader efforts beyond the biotechnology industry, as protocol development within a company is clearly viewed as competitive and proprietary.

2. A second consideration when it comes to the cost of phase 3 trials is the increasing complexity in design of modern clinical trials. For instance, a recent study out of Tufts showed that the number of endpoints and procedures in clinical studies has gone up by more than 60% from 2002 to 2012. At the same time, this study showed that a minority of the procedures, endpoints and related trial costs in phase 3 trials are driven by regulatory requirements. Non-core elements of these trials were estimated in this study to total in the range of 4-6 billion dollars of aggregate spend across the industry.[iv] This trend to increasing complexity is reflective of the fact that modern trials are designed to address an increasing number of demands (e.g., differing regulatory demands across regions, differing payer expectations, addressing marketing claims, new exploratory science/endpoints, interests/input of key opinion leaders, etc.). While some

of the increase in complexity may be an unavoidable cost of modern drug development, some of this is self-inflicted and can be addressed by sponsors through purposeful efforts focused on designing efficient, focused and feasible trials. While interdisciplinary oversight committees aimed at achieving simplified, efficient trial designs are being implemented by some sponsors, I believe this is still not the norm. I further think that such efforts should be encouraged by FDA during end-of-phase 2 discussions with sponsors. I should point out, however, that while FDA has much expertise in review and regulatory oversight of clinical trials, there are very few people within the FDA who have had practical experience in clinical trials planning and operations. Therefore, while it would be advantageous to have FDA take this on as a part of their mission, very few within the Agency truly understand in detail the demands and drivers of trial planning and conduct with the kind of granularity necessary to serve as effective advisors and advocates for decreasing complexities of clinical trials. In other words, were FDA to take on this role more actively, they would need to recruit and/or develop the requisite expertise.

3. A third consideration in reducing clinical trial expenditures is moving further away from the past paradigm of regarding face-to-face clinical evaluations as the gold standard of patient evaluation. There is an increasingly sophisticated ability to assess patient status and to accrue sophisticated clinical data via new technologies, technologies that integrate accurate patient-based assessments with the ability to collect and transmit real-time data. Yet, these technologies have yet to reach full fruition as fundamental elements of phase 3 trials. There is a tremendous opportunity to incorporate into modern trial designs an approach that replaces some or in some instances even all patient visits to investigative sites with the use of "at home" assessments. For this to be fully implemented, FDA itself will need to continue to participate in discussions on important issues such as device approval status, measurement properties (e.g., accuracy and precision), data

integrity given the real time accrual of data and lack of written source records, and means to ensure patient privacy. While some elements of patient-based electronic data generation and capture have become routine, these technologies and approaches are ripe for broader use and doing so could lead not only to more efficient trial designs, but arguably more accurate data. For instance, an increase in the frequency of assessments can lead to better precision in estimating treatment effects. All of these enhancements could replace patient evaluation visits and thereby save clinical expenditures and alleviate patient burden (perhaps then enhancing recruitment).

4. Two other considerations that have been much discussed and oft times debated in this vein include increasing the regulatory acceptance of adaptive trials, as well as the need for efforts to spur the development of new means endpoints (such as new surrogate measures and/or new patient-reported outcome tools). Let me briefly touch on both.

    a. While adaptive designs are increasingly common in drug development, they have been most commonly implemented in the design of earlier phase studies, where the scientific "risks" are borne more by the sponsors than the public and/or regulators. There are fewer successful examples of effective use in late phase 2 and phase 3. I believe this reflects the reality that the pluses of adaption (speed, efficiencies) are traded off with complexities in design, conduct and interpretation. One especially notable hope for adaptive designs is the idea of eliminating development "white space" through the use of what is termed a seamless phase 2-3 trial – trials where a successful phase 2 study transitions automatically into phase 3. While this sounds attractive, this kind of adaptive trial raises many significant issues – not the least of which is the loss of the ability to conduct a true "learn and confirm" development paradigm, which is the very

heart of cogent drug development. If there is any message in the rising failure rate of phase 3 trials, I think it is that the increasingly parallel drug trials paradigm (rather than the serial learn-and-confirm model) does not allow for enough careful thought of past results to properly inform future designs.

b. On the topic of new endpoints, there is little debate about the need for such – particularly in areas of unmet medical need. For many areas of unmet need, the uncertainties on regulatory pathway, including the absence of acceptable endpoints, are substantial impediments to develop of new therapeutics. Yet developing and validating new endpoints, such as validated surrogate assessments and/or patient-reported outcome instruments is complex and too time consuming. While developing new surrogate endpoints and patient-reported outcome instruments to the point of regulatory validation is broadly supported, an important question is how to best drive this process scientifically and practically. While the FDA must be involved in these efforts, FDA is not best equipped to drive the efforts from either the perspective of having the resources to do so or the requisite expertise. While Public-Private partnerships can succeed, a recent experience with a specific program – the EXACT-PRO initiative[v] – demonstrates how long and arduous this can be (the EXACT-PRO initiative began in 2004 during my FDA tenure but only resulted in the FDA regulatory guidance declaring it sufficiently validated nearly a decade later[vi]). As with many of these issues, a more concerted, broader effort would be needed to address this need systemically with a goal towards the timely development of endpoints in targeted areas with the greatest need for such.

In closing, let me say that I believe that efforts to modernize clinical trials are critically important as a part of the broader discussions on how to advancing innovative therapeutics. I further believe there is much that can be done to

achieve better efficiencies in drug development without undermining the traditional paradigm of requiring "substantial evidence of effectiveness" prior to regulatory approval. The thorough evaluation of safety and efficacy is critical safeguard to patients within the US since it assures that new therapies are convincingly shown to have a favorable risk-benefit profile via well-conducted randomized controlled trials. I would also add that the current regulatory/development system, inefficient as it may be, still leads to innovative drugs being available first to the US market more often than any other market globally[vii] and these FDA approval decisions are regarded as a reference standard to many regulators across the globe. At the same time, the increasingly daunting costs faced by sponsors in conducting phase 3 trials and the impact on the sustainability of therapeutic development is undeniable. Therefore, a systematic and systemic effort undertaken in collaborations across government, industry and the public sector is needed, all with the goal to apply best thinking and practice to the achievement of efficient, modern clinical trials.

Thank you for this opportunity to participate in this hearing.

[i] Roy, Avik Project FDA Report: Stifling New Cures: The True Cost of Lengthy Clinical Drug Trials. Manhattan Institute for Policy Research, #5: April 2012

ii Hay, et al. Clinical development success rates for investigational drugs, *Nature Biotechnology 2014* 32, pp 40–51

[iii] A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program; http://iom.edu/Reports/2010/A-National-Cancer-Clinical-Trials-System-for-the-21st-Century-Reinvigorating-the-NCI-Cooperative.aspx

[iv] Getz, K "Improving Protocol Design Feasibility to Drive Drug Development Economics and Performance." Int. J of Environ. Res. Public Health, 2014, 11: 5069-80

[v] http://www.exactproinitiative.com/

[vi] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM380961.pdf

[vii] http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm276385.htm