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HUNTINGTON'S DISEASE REGULATORY SCIENCE CONSORTIUM (HD-RSC) KICKOFF MEETING

Sheraton Silver Spring, MD
November 6-7, 2017

The following is an overview of the Huntington's Disease Regulatory Science Consortium (HD-RSC) kick-off meeting. The 2-day meeting, generously funded by CHDI Foundation, brought together a diverse range of participants representing the pharmaceutical industry, academic opinion leaders, regulators (FDA and EMA), and patient advocacy groups in a variety of platform talks, panel discussions, and breakout sessions. Complete meeting materials, full agenda, list of participants, as well as the slides for all presentations and sessions are currently available upon request, and will be posted for HD-RSC member access shortly.

Meeting Objectives

The key meeting objectives were to:

1. Solicit input from stakeholders on the need and potential impact of a dedicated regulatory science consortium for HD.
2. Develop an understanding of the value of a pre-competitive consortium model to advance regulatory science that can enable Huntington's disease (HD) Drug development.
3. Communicate the importance of data contribution towards advancing regulatory science in HD.
4. Engage in networking and dialogue to actively seek input on their needs from members of this new consortium.

The breakout sessions on the second day of the meeting included: Model-Based Strategies for Clinical Trial Enrichment: Focus on Biomarkers, Clinical Outcome Assessment Measures in HD for Use in Trials, and Therapeutic Development in Pre-Manifest HD: Opportunities and Challenges.

Day 1: November 6, 2017 HD-RSC Kickoff

The Vision: CHDI's Dedication to Successful HD Treatments

Robi Blumenstein, CHDI Foundation (*President*)

"It will take a true collaboration to move forward."

Immediately, the group was challenged to change from thinking in terms of HD treatments, cures, and disease modification to the more ambitious goal of prevention. The HD field has the unique advantage of knowing the causative genetic mutation. To properly leverage this knowledge, share learnings, and deliver effective drugs to patients who desperately need them, academic and clinical researchers, drug developers, and trial participants must come together. By accessing and using existing clinical data, such as from the Enroll-HD trial, the community will be able to capture relevant clinical outcomes throughout disease stages and apply to future clinical programs. This will be especially critical for identifying and classifying early and even premanifest stages of the disease, where gene-positive patients may not yet be exhibiting clinical symptoms but disease-relevant information (such as CAG length) can be gathered to develop early disease biomarkers.

Essential to the overall goal of accelerating time to delivery of treatments to patients, the HD-RSC is designed to allow discussions with regulators on what needs to be done to show a treatment is ready for

market. However, active pharmaceutical company contribution, ready involvement, and feedback is required throughout the processes to ensure success.

Consortia-Based Strategies in Neurodegenerative Diseases: Critical Path Institute's Track Record in Collaborative Efforts.
Martha Brumfield, Critical Path Institute (*President and Chief Executive Officer*)

"All participants share the risks, but also share in all the benefits!"

C-Path acts as a trusted, neutral third party that works to convene members of industry, academia, and government for sharing of data and expertise. The consortium platform enables iterative engagement of members with regulators, including EMA/FDA/PMDA, enabling regular feedback and input to accelerate time to regulatory acceptance and readiness of drug development tools within a given therapeutic area.

The overall focus of the HD-RSC is to promote the development of innovative drug development tools to be incorporated into regulatory approaches critical for advancing safe and effective HD therapies. It is not the purpose of the consortium to participate in efforts to advance single products, therapies, or clinical programs, or to enable a single member to succeed above others. Rather, HD-RSC will enable protected mechanisms for information and data sharing among consortium members and will foster awareness of the importance of data standardization. Successful data sharing for the consortium will require developing data standards for the HD field as well as bringing patient level data together in an appropriate and consistent format. In contributing to HD-RSC, consortium participants accept that there are shared risks, but also accept they will share in the benefits of the work done.

Defining the need. What are the key challenges for Drug development in HD?
Moderator*:* Jeff Carroll, Western Washington University (*Associate Professor, Department of Psychology*)
Panelists: Mike Panzara, Wave Live Sciences (*Franchise Lead, Neurology*), Scott Schobel, Roche (*Translational Medicine Leader*), Louise Vetter, HDSA (*Chief Executive Officer*), Juliana Bronzova, EHDN (*Science Director*), Mark Gordon, Teva (*Senior Director, Clinical Development*)

Industry leaders and representatives came together in this panel to weigh-in on the biggest challenges facing the community, noting a commitment to patients and families above all else. It is our duty and responsibility to the HD community, they said, to make the best use of patient data. The HD clinical research community should ensure that the maximum amount of knowledge is extracted from patient data, and that as the science behind drug development becomes increasingly complex, we must also provide education and guidance on participation in clinical trials, with specific attention given to helping patients understand trial enrichment criteria and eligibility.

Industry leaders urged the group to work together to enhance the sensitivity of clinical outcomes and to identify biomarkers with clear clinical relevance to de-risk and accelerate drug development, two cornerstones of the HD-RSC. Key gaps or needs from trialists identified by the group are to develop sensitive, disease stage specific measures to enhance trial efficiency, and to agree on industry standards for fluid biomarkers. The group highlighted that the ability to reliably measure mHtt in the CSF as well as imaging techniques for neurons and brain regions affected are already in development, but more work is required to prove their utility to act as surrogate or as predictive biomarkers. The prospects for Huntingtin (Htt) lowering therapies seem promising, and the consortium can work to gain further clarity on whether Htt is a good target for drug development. Further, the development of surrogate endpoints will reduce the numbers of patients required for clinical trials, recruitment of whom will be of increasing significance as clinical programs begin to rapidly advance. A key question for pharmaceutical development is which functional and/or global outcome measures regulators would accept as a patient focused outcome.

All agreed that there is no time to waste, as many candidate therapies are reaching the clinical development phase and industry standards across biomarkers, data standards, trial simulation tools, and clinical outcomes are needed to address the urgent needs for effective treatments.

Regulatory Impact for Huntington's Disease: FDA & EMA Perspectives.
Billy Dunn, FDA (*Director, CDER*, *Division of Neurology Products*)
Manuel Haas, EMA (*Head of CNS, Evaluation Division*) (Remote)

The FDA and EMA both echoed the idea that the focus of the HD research should be prevention of the disease, as the most successful treatments will treat the underlying pathology and early intervention will have the greatest impact for HD families. Harmonization between the EMA and FDA is key to make the best use of a limited population base. There are already joint procedures in place, with regularly scheduled discussions. Both agencies also emphasized the role of consortia for advice to stakeholders, with the EMA pointing out that the consortium can also provide valuable advice, feedback, and education to the regulators on the disease.

The FDA emphasized that they see data sharing as pivotal in the success of the HD-RSC and the field overall. From the FDA perspective, the HD-RSC provides a venue to and conversational space for precompetitive collaboration to the benefit of all, and that all participating companies should embrace the opportunity for data sharing. Further, the agencies aligned on key deliverables for success, including obtaining a detailed understanding of disease progression in the very early disease stages, identification of targets and relevant biomarkers to confirm target engagement, and incorporation of standardized assessments into routine care and clinical research to enable aggregation of data for further unbiased exploration. Further, the development of progression models and clinical trial simulators will provide critical information on the sample sizes and outcomes needed to show a relevant effect and will improve trial efficiency through identification of suitable subgroups. Above all, though, is the importance of the patient voice. In the case of HD, it is important to remember that the caregivers may well be HD gene carriers themselves, and their feedback may prove quite important in assessing cognitive impairment.

Model Informed Drug Development.
Issam Zineh, FDA (*Office Director, Office of Clinical Pharmacology*)

Defined as the *"development and application of pharmaco-statistical models of drug efficacy and safety from preclinical and clinical data to improve drug development knowledge management and decision-making,"* model informed drug development is recognized and valued by the FDA as a pathway to reduce uncertainty. The guidance provided by such modeling is considered especially useful where trials are unavailable or are unlikely to be performed, such as in rare genetic diseases like HD, and the use of modeling is now mainstream in the FDA to inform decisions. Further, the most recent update of the Prescription Drug User Fee Act (PDUFA-VI) covering the fiscal years 2018-2021 incorporates many aspects of modeling. Regulatory decision tools now incorporate model informed drug development, complex innovative trial designs, formalization of biomarker qualification, real-world evidence, benefit/risk assessments, and a program for community engagement to understand the patient voice.

Previously, in 2010, the FDA published a regulatory science document, which had a vision that reinforces the need for collaboration. Of direct relevance for HD research and development, topics include: developing better models of human adverse response; using and developing computational methods and in silico modeling; leveraging existing and future clinical trial data for disease progression modeling; identifying and qualifying clinical and non-clinical biomarkers; developing and refining clinical trial designs

and endpoints; analyzing large scale clinical and preclinical datasets; and developing and applying simulation models for product lifecycles, risk assessment, and further regulatory science use.

From Model-based Clinical Trial Enrichment to Comprehensive Clinical Trial Simulation.
Brian Corrigan, Pfizer (*Vice President, Global Head, Clinical Pharmacology*)

Researchers were warned to be prepared for the "data tsunami" inevitably produced by applying modeling methods. The resources required to interrogate and understand all the data requires a concerted effort, and is usually bigger than individual organizations can manage. In this respect, the development of data standards is key in bringing what is often a collection of disparate legacy data into an integrated dataset. This is essential in disease progression modeling, where a base model characterizes a given disease's natural time profile, and changes due to active treatment are superimposed onto the base model to simulate the effect of a drug on the disease. The model can then be used to evaluate the impact of factors such as dropout, and various scenarios can be tested (e.g. more/less subjects, different inclusion criteria, shorter/longer study durations) until an optimal study design is found for the current stage of drug development.

Importantly, the FDA, in collaboration with C-Path, pioneered the pathway for regulatory acceptance of model based drug development tools, and HD-RSC can benefit from key learnings. The HD-RSC brings together all the ingredients for a successful collaboration, including a knowledgeable team, previous consortia experience, rich data sources, understanding of data standards, emerging approaches to therapy, innovative analysis techniques and tools available, and a clear regulatory path.

Developing a Comprehensive Quantitative Description and Understanding of Disease Progression in Manifest HD. Success in Sharing Data from HD Natural History Studies.
Amrita Mohan, CHDI Foundation (*Director, Clinical Bioinformatics*)

"Data sharing is possible and it is well demonstrated that this sharing improves accuracy and improves research."

HD natural history studies are important to guide clinical development but face several specific challenges, namely the subtlety of early symptoms, the sparse population, and the current lack of progression biomarkers. To date, there have been 15 natural history studies in HD. The HD-Natural History (HD-NH) project has combined data from 4 large observational studies (TRACK, REGISTRY, PREDICT, and ENROLL). Together, the trials include >20,000 participants (HD gene carriers and controls) with a median of 2 visits (range 1-17 visits), and the data includes >2000 outcome measurements (e.g. UHDRS assessments) and >100 fixed variables (e.g. CAG length, demographics). Proper integration required extensive quality control, and both quality control and legal issues would have been eased through the implementation of data standards. At present, this rich dataset has been used to develop a model of 9 distinct clinical events spanning 4 decades from early premanifest to symptomatic HD. These events are measurable using established tests, making them directly relevant to current clinical practice.

HD Progression Modeling. Aligning Data with Context of Use Applications.
Moderator*:* Klaus Romero, Critical Path Institute (*Director, Clinical Pharmacology and Quantitative Medicine*)
Panelists: Brian Corrigan, Pfizer (*Vice President, Global Head, Clinical Pharmacology*), Bernhard Landwehrmeyer, Ulm University Hospital (*Professor of Neurology "Clinical Neurobiology," Department of Neurology*), Kevin Krudys, FDA (*Lead Pharmacologist, CDER, Division of Pharmacometrics, Office of Clinical Pharmacology*), Gerald Podskalny, FDA (*Medical Officer, CDER, Division of Neurological*

Products), Charles Venuto, University of Rochester (*Clinical Pharmacologist, Department of Neurology in the Center for Human Experimental Therapeutics*)

The panel focused on the development and application of the context of use (COU) statement, noting that this sets the context for how the FDA will review an application. A clear statement helps all stakeholders understand the deliverables required at each stage of development. Panelists cautioned that it is important that the statement sets reasonable expectations of what the dataset can offer and within a reasonable timeframe, adding that a COU can start small and be updated accordingly. Stakeholders should embrace a learn and confirm process, allowing for evolution and refinement of the context of use statement. Project plans should include communication and training of the community in how to use the developed tool, as well as feedback on how tools should be adapted or if new tools are needed. The HD-RSC will play an essential role in overcoming company anxiety about sharing data and help with the realization that even so called 'failed' studies provide useful data. It is important that all data is clean and interpretable, and ensuring the validity of data at collection will mean that the value of the data will live on and can be used when the field is ready to interrogate new questions. Further, the development of an HD therapeutic area specific user guide comprised of consensus data standards will enable comparability of studies such that they can be easily integrated into clinical development models. Good models require several iterations between the original context of use statement and the eventual modeling framework. However, scientific validity should predefine the questions to be asked and definitions of success.

It was noted that the FDA views modeling tools as a starting point, and not as an endpoint themselves. However, FDA endorsement of quantitative tools should give confidence for pharmaceutical companies to move forward with their clinical research. Tools can be used to approach regulators when explaining why a potential trial design is considered most appropriate for a research question. The consistent use of new tools will also help regulators and pharmaceutical companies to 'speak the same quantitative language,' thereby providing a clarity of thinking.

Rationale and Impact of Building a Comprehensive HD Clinical Database.
Cristina Sampaio, CHDI Foundation (*Chief Medical Officer*)

The vision for a comprehensive HD database is one that utilizes CDISC standards to ensure ease of use and minimize errors, quality controlled to ensure data accuracy, includes a large number of patients, and spans the entire spectrum of HD stages. A true comprehensive database should include clinical outcomes in all the relevant domains of the disease (motor, cognitive, and behavioral) and is informative at many levels, not least in terms of participant characteristics to identify genetic modifiers in the CAG code that have relevant effects on prognosis. Future genotyping for information on modifiers will allow stratification of modifiers into clinical trials. However, few studies have been done to support prognostic biomarkers and almost none supporting predictive biomarkers. Likewise, there are no comparative studies of placebo response across studies, essential to establishing the rates of decline and not just improvement under placebo. The HD-Natural History dataset is a success, but is not yet comprehensive. Once compiled, a fully comprehensive database will be informative in describing the natural history of HD through clinical outcomes and biomarker data, will help delineate the placebo effect, and eventually will help understand response data to specific interventions. For HD-RSC to succeed, all consortium members must further this work by supplying the necessary trial data, including the rarely shared data from placebo arms.

Biomarkers as Tools to Enable Decision Making in HD Drug Development.
Eric Siemers, Eli Lilly (*Distinguished Medical Fellow,* Alzheimer's Disease Platform Team)

While the different disease stages (e.g. preclinical, prodromal and mild) are operationalized for clinical trials, the lines are usually more blurred in clinical practice. However, it is important to recognize that

appropriate outcome measures must be established for each group of patients. Experience in Alzheimer's disease drug development has taught us that proving target engagement is a vital step in a clinical trial program. Of all the potential disease-modifying drugs for Alzheimer's disease, only those which showed target engagement and an effect on Aβ have had any measurable effect in Phase III studies. However, showing target engagement is not enough. It is also helpful to perform exploratory studies to understand the utility of other measurements, such as was the case for temporal lobe volume in AD. Most importantly, it is essential to choose analysis methods carefully, so as not to over-interpret findings or under-estimate efficacy.

Clinical Outcome Measures in HD: Beyond UHDRS.
Glenn Stebbins, Rush University (*Professor, Department of Neurological Sciences*)

Originally published in 1996 and revised in 1999, the UHDRS is a clinician rated outcome that assesses the motor, cognitive, behavioral and functional capacity of a person with HD. However, the UHDRS was developed without HD family involvement or cognitive pre-testing. As a result, the clinimetrics of the motor scale are stronger than the behavioral, functional, and cognitive scales. These limitations have led to the development of the HD-Cognitive Assessment Battery (HD-CAB) for a comprehensive assessment of cognition in HD, and modification of existing scales (combined HADS/Snaith Irritability Score) or introduction of new scales (PBA-s or FuRST-HD) for behavioral and functional assessment. These scales have their own limitations, including an impact of language translation on the combined HADS/SIS assessment and unreliable factor structure in the PBA-s. These scales suffer from issues in the scale development process including failure to define the domains of interest by not engaging with clinicians, patients, caregivers, other stakeholders, assessment source (e.g. should the outcome be patient reported given insight limitations or clinician rated given they cannot know all events), and scaling approach (e.g. summary, additive, multiplicative). Thus, a strong commitment to the scale development methodology is required. An understanding of the limitations of the various outcomes is required when interrogating databases of data, such as that provided using wearable technologies in the future.

Outlining a Roadmap for Clinical Trials in Pre-Manifest HD.
Moderator*:* Karl Kieburtz, University of Rochester (*Professor of Neurology*)
Panelists: Steve Hersch, Voyager (*Senior Director, Clinical Development*), Billy Dunn, FDA (*Director, CDER, Division of Neurology Products*), Eric Bastings, FDA (*Deputy Director, CDER, Division of Neurology Products*), Bernard Ravina, Voyager (*Chief Medical Officer*)

Before performing clinical trials in the pre-manifest HD population, companies first need to gain a better understanding of the incentives and challenges for this population in clinical trials. By conducting trials in premanifest disease, one can expect a more robust effect. However, the need to enrich for 'close to onset' patients is a significant confounder to moving even earlier in the disease. The key issue then, is to understand not only the evolution of HD but the behavior of the various biomarkers over time, how they relate to brain levels, and their relationships with clinical outcomes at different disease stages. This information will aid clinical trials by identifying early disease states, separating HD gene carriers into categories, and developing more sensitive outcomes to evaluate impact on subtle changes.

With several biomarkers already in development, panelists agreed that mutant HTT has already passed the first test of biologic plausibility, although better understanding of how it behaves over time and in response to intervention is urgently needed. Further, the group agreed that showing a pattern of effects on biomarkers is more convincing than effects on a single biomarker, provided there is consolidated understanding of the biology. Handling these large amounts of data and filtering signal from noise can be hard to do as a single entity, further highlighting the need for data sharing in the success of HD-RSC. Data sharing will provide the increased power required to assess new theories and broaden current categorical

constructs for symptomatic disease progression. All agreed that for success of the consortium, however, it is vital that scientific integrity is not compromised by sharing data, particularly relevant for ongoing studies.

The panel touched on the priority need for biomarkers with respect to the accelerated approval process, which allows approval when it can be concluded that a change in a biomarker, surrogate, or intermediate will result in something clinically meaningful. A suggested alternative pathway to approval is to perform 'time to' milestone analyses. However, these are dependent on a strong understanding of the underlying natural history of disease and involve very long studies- time the field simply does not have. Regulatory representatives advised that when the development of a devastating disease is a certainty, as is the case for HD, this is taken into account in the regulatory pathway. The decision to treat a young person in a pre-manifest stage requires its own considerations based on the benefit-risk ratio of each drug. The HD-RSC needs to seek guidance from HD families regarding their risk tolerance in moving pre-manifest trials forward while providing a clear informed consent process.

The Impact: Why This Matters to Patients.
Charles Sabine, Patient Advocate (*Former Emmy-awarded NBC News journalist and high-profile spokesman for the global HD community)*

Closing Day 1 of the meeting, Charles Sabine urged the members of the consortium to come together to meet the needs and expectations of families living with HD. He explained that families are more interested in something that works, than perfect data. People impacted with HD need hope and they are waiting for a collaboration to work on how to manage the problems they face with HD.

"We have hope, but hope can only be built on the trust that everyone is working as fast as they can in the same direction."

LINK TO VIDEO:

https://c-path.org/hd-rsc-kick-off-charles-sabine-presentation/

Day 2: November 7, 2017 HD-RSC Kickoff

The Operations: How HD-RSC Would Work
Diane Stephenson, Critical Path Institute (*Acting Director, Huntington's Disease Regulatory Science Consortium* (*HD-RSC) and Executive Director, Critical Path for Parkinson's* (*CPP*) *Consortium*)
Debra Hanna, Critical Path Institute (*Executive Director, Critical Path to TB Drug Regimens* (*CPTR) Consortium*)

The proposed governance of HD-RSC is aligned with other C-Path consortia, and will include representatives from all types of stakeholders. Thanks to the generosity of CHDI Foundation, the HD-RSC consortium will operate under a single funder model. A core leadership team will consist of the C-Path Executive Director, CHDI Foundation Director, an Industry Representative, and an Academic Representative. Successful organizational principles are established to enlist members to a universal legal membership agreement. This defines the rules of engagement including terms and conditions, expectations of the members, confidentiality governance principles, and publication guidelines. All HD-RSC members will be asked to sign a legal membership agreement to participate in the consortium.

The actual work of the consortium will be carried out by individual working groups. Most teams will meet monthly via teleconference, with face-to-face meetings taking place annually and, at times, in conjunction

with relevant conferences where members are present. In surveying the unmet needs from the field, five working groups have been proposed:

1. Data Inventory
2. Modeling Inventory
3. Biomarker
4. Clinical Outcome Assessment
5. Regulatory Science Forum

The teams will work closely together as there are interdependencies for enabling each other's goals. Up to two individuals from all member organizations are invited to participate in monthly coordinating committee meetings to review the progress of the consortium.

Several operational insights can be gained from the Critical Path to TB Drug Regimens consortium at C-Path, a successful example of a large global single funder model fully funded by the Bill and Melinda Gates Foundation. The development of CDISC foundational data standards was the first success for CPTR, and CPTR found early success through educational initiatives and stakeholder engagement. Additionally, a strong focus on modeling and simulation is fundamental to the strategy of the 7 CPTR working groups. Of interest to HD-RSC, the consortium has 3 data platforms, each with tiered access based on the data owner's specifications. HD-RSC stakeholders emphasized that continued stakeholder engagement, tiered data access, and focused sub-teams within large working groups were all of interest for further discussion.

It was noted that the consortium provides a platform to accelerate reviews of individual sponsors coming to them for review. New scales can be proposed without the need for full outcome measure qualification, and the FDA advocates for "regulatory acceptance" of scales and Clinical Outcome Assessments (COAs) rather than a focus on qualification. Innovation can still happen at the individual sponsor level without the requirement for the consortium to achieve consensus from all stakeholders. It was emphasized that the goal of the consortium is not necessarily consensus but rather collaboration, where consensus refers to reaching agreement on what will be done, while collaboration involves listening to others to identify what opportunities exist and include new ideas and recommendations into the consortium.

Introduction to Breakout Sessions

The purpose of the breakout sessions is to have a forum of smaller focused groups to encourage open dialogue amongst the many esteemed experts who attended this kickoff. There is no intent to lay out prescriptive plans for the consortium in these sessions nor in the preliminary consortium research plan (CRP) shared with participants in advance of the meeting. The true spirit is to encourage open discussion, sharing of ideas and simply get to know each other in person. Each breakout is facilitated by a representative from CHDI Foundation, C-Path and an academic expert who engaged in preparation activities to share some ideas and slides with attention to data (as opposed to theoretical ideas). C-Path is applying learnings from other consortia to focus on the development and alignment of key "go forward" plans through effective listening and communication.

The three breakouts were chosen to align with three of the five proposed working groups for the new HDRSC consortium (see CRP and governance slide). The summaries of the individual breakout sessions can be found in Appendices A-C, respectively.

1. **Model-based Strategies for Clinical Trial Enrichment: Focus on Biomarkers**
2. **Clinical Outcome Assessment Measures in HD for Use in Trials**
3. **Therapeutic Development in Pre-manifest HD: Opportunities and Challenges**

A brief discussion facilitated by Dr. Billy Dunn focused on the Consortium for Alzheimer's Prevention (CAP) took place to provide learnings that may facilitate the progress of HD-RSC. The publication by Weingard et al. 2016 (*Alzheimer's and Dementia* 12: 631-632), was distributed to all participants as a handout on Day 2. Participants were directed to key highlights of this initiative with relevance to HD, including standardizing data acquisition when possible, encouraging sharing of both data and samples, inclusion of multiple exploratory biomarkers in clinical trials, sharing of baseline data within 12 months of enrollment in trial, long term continuation to confirm clinical benefit after an accelerated approval and sponsors to ensure that informed consent at enrollment is aligned with sharing of data and samples at study completion. The principles outlined in the CAP initiative align and meet the current needs of the HD field where numerous trials are advancing in this limited patient population.

Next Steps

The immediate next steps are to send out legal agreements for members to sign onto the consortium. C-Path will prepare a meeting summary as well as a proceedings manuscript that captures the meeting at a high level. This documentation will take a few months but willenable the initiation of the working groups in early 2018.

Conclusions

Cristina Sampaio, CHDI Foundation (*Chief Medical Officer*)

Key highlights for HD-RSC to have impact include the need for data sharing, the importance of focusing on prevention and the urgent need for advancing biomarkers for use in trials. The concept of harmonization between FDA and EMA is also extremely valuable and will aid in accelerating treatments at a time when numerous therapies are advancing to the clinic. Modeling approaches will be a key focus for the consortium, yet it is important to keep in mind that models are a process-to-an-end and help define the rules to get to final common goals. The needs in the biomarker space are great. Most of the focus to date has been on biomarkers of disease progression yet there are limited examples of prognostic and predictive biomarkers. The themes that have been emphasized at the HD-RSC kickoff meeting are truly needed for HD therapies to reach the patients in need.