CRITICAL PATH INSTITUTE

REGULATORY SCIENCE FRAMEWORK OF DRUG DEVELOPMENT TOOLS

Version 2.0

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CHAPTER 1: INTRODUCTION TO THE CRITICAL PATH INSTITUTE REGULATORY SCIENCE FRAMEWORK OF DRUG DEVELOPMENT TOOLS

1.1 WHY DO WE NEED A REGULATORY SCIENCE FRAMEWORK OF DRUG DEVELOPMENT TOOLS?

There is a collective understanding that no single entity or organization can bring about meaningful transformations to the medical product development process alone. New drug development is a complex and expensive endeavor that often takes decades to identify an ideal drug candidate and complete clinical trials that support a regulatory application.[1] There is a need for well-orchestrated collaboration amongst relevant actors, including industry, patient groups, academia, and regulators. The Critical Path Initiative of 2004[2] was a call to action for innovation and acceleration of the development of U.S. Food and Drug Administration (FDA) regulated medical products. The Critical Path Opportunities List,[3] published in 2006, described specific areas of needs and priorities for the agency. The need to advance regulatory science to help drive regulatory decisions and accelerate medical product development has been outlined in FDA reports such as the 2004 Critical Path Initiative,[2] the 21st Century Cures Act of 2016,[4] and the 2022 FDA Focus Areas of Regulatory Science (FARS).[5] In addition, the Prescription Drug User Fee Act (PDUFA) VII Commitment Letter[6] outlined priority areas, including translational science to advance the use of biomarkers and drug development tools (DDTs) for rare and orphan diseases, the use of real-world evidence (RWE) and artificial intelligence (AI) in regulatory decision tools, use of model-informed drug development (MIDD), and incorporation of the patient's voice in patient-focused drug development (PFDD), as well as enhancing drug development through innovation in cell and gene therapy.

Similarly, the European Medicines Agency (EMA) published a report in 2021 on Regulatory Science Research Needs which outlines the gaps in regulatory science to improve medicine development and evaluation.[7] This EMA report identified over 100 topics, such as validation of surrogate endpoints and biomarkers, predictive analytics to inform risk management, development of novel approaches and modeling to reduce animal testing, and utilization of real-world data, artificial intelligence and machine learning in regulatory decisions, with the intention of stimulating researchers and funding organizations to work towards addressing these challenges and accelerating medical product development. The EMA launched the European Platform for Regulatory Science Research in 2025 to foster interdisciplinary collaborations and meet the objectives of accelerating regulatory science research, increase the quality

and impact of research and improve regulatory practices, standards, development and use of medicinal products.[8]

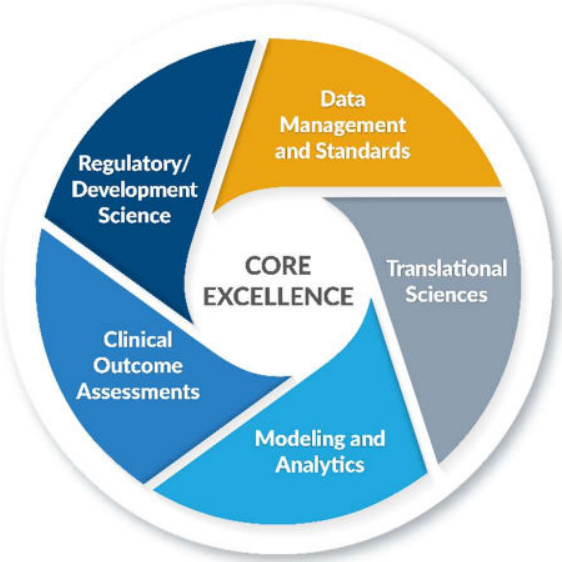
Despite these initiatives and recently created centers of excellence, overarching programs, and innovation hubs, the development of DDTs remains a resource-intensive process for stakeholders. While both FDA and EMA support stakeholder engagement and welcome "the **sharing of results and data** with potential public-health impact by researchers, even before these have been published in a peer-reviewed journal,"[8] there remains a need in the drug development enterprise for (1) quality control and standardization of evaluation tools such as biomarkers, (2) benefit-risk management for patient safety, (3) streamlined processes and adoption of tools for efficient drug development, (4) clear and transparent regulatory guidance, and (5) investment to advance science and technologies. A framework outlining the development of DDTs may offer insight into the process and allow regulators and other stakeholders alike to integrate learnings. With 20 years of experience convening public-private partnerships (PPPs), Critical Path Institute (C-Path) is in a unique position to create a knowledge management framework to capture and share learnings across diverse therapeutic areas including neurodegenerative disease, chronic conditions such as type 1 diabetes, heart failure and major depressive disorders, rare and orphan indications, and pediatric disorders. This regulatory science framework culminates from the collective learnings by C-Path that may offer insight into the processes for regulatory considerations and allow drug developers, regulators and other stakeholders to integrate these learnings. The goal of this framework is to de-risk drug development, promote collaborative innovation, and accelerate drug development by outlining standards and evidence for evaluating development tools, sharing regulatory outcomes to reduce uncertainty, and encouraging adoption and implementation of novel tools. As drug development is not a static process, new scientific discoveries, advanced technologies, and knowledge of disease pathophysiology will add to the learnings from this framework and drive future collaborations to address critical unmet medical needs and improve public health.

About Critical Path Institute (C-Path)

C-Path was founded in 2005 as a nonprofit public-private partnership under the auspices of the FDA's Critical Path Initiative and launched its European nonprofit office in the Netherlands in March 2022. C-Path's mission is to advance medical product development through the generation of solutions that aid in the scientific development and evaluation of new medical products. C-Path consortia and programs work to solve drug development challenges in both specific disease areas as well as across multiple

methodologies that are disease agnostic. Since C-Path's inception, there has been, and continues to be, a growing need to optimize the regulatory review process of novel medical products and bring them to patients faster and more efficiently. Built upon its foundation as a neutral convener, C-Path has established core competencies in **data management and standards, modeling and analytics, regulatory/development science, clinical outcome assessment (COA) and translational sciences** (see Figure 1), which are deployed across disease-specific and disease-agnostic initiatives. C-Path employs a collaborative approach to improve drug development by aligning stakeholders around key challenges and developing solutions together. This work has produced tangible outcomes including COA tools, clinical trial simulators, biomarkers, data resources, and analytic platforms.

Figure 1. C-Path's Core Competencies



1.2 HOW TO USE THIS FRAMEWORK

The Critical Path Institute's Regulatory Science Framework of Drug Development Tools, hereinafter the Framework, is designed to provide detailed guidance on how C-Path generates regulatory-grade solutions for unmet needs in drug development. Through the lens of C-Path's 20 years of experience and selected regulatory examples, this Framework will explore how an unmet need is identified, how context of use (COU) is defined, how supporting evidence is developed, and how regulatory science solutions and regulatory strategies are developed. The final chapter will address the scalability and

future uses of the Framework to accelerate drug development. The Framework is applicable to evaluation tools seeking endorsement from regulatory authorities.

A decision tree (see Appendix 3) has been developed concurrently with the Framework to elucidate the processes that should be considered for decision-making during drug development. The decision tree aims to capture key questions and go/no-go decisions discussed among C-Path consortia and programs when generating novel DDTs. While this process is depicted sequentially within the decision tree, each DDT case is unique and may not follow this order. Additionally, novel questions may arise as needs change within the development process. Thus, the Framework and the DDT decision tree are living documents that will continue to evolve.

In the interest of simplicity, funding will not be addressed in this Framework. Funding is a key component across the continuum of DDT development and serves as a barrier along each step of development. Despite its importance, obtaining and maintaining funding is out of scope for this Framework.

CHAPTER 2: A FRAMEWORK OF LEARNINGS: HOW DO WE GENERATE REGULATORY-READY SOLUTIONS?

2.1 IDENTIFYING AN UNMET NEED

Identifying the unmet need is a crucial first step in the DDT process. An unmet medical need is defined by the FDA as "a condition whose treatment or diagnosis is not addressed adequately by available therapy. An unmet medical need includes an immediate need for a defined population (i.e., to treat a serious condition with no or limited treatment) or a longer-term need for society (e.g., to address the development of resistance to antibacterial drugs)."[9] This includes situations where existing treatments are inadequate or where there's a need for a new treatment approach for a specific disease. The unmet need is first identified from a call to action, which may come from external stakeholders such as regulatory bodies, patient groups, pharmaceutical industry members, or academia. A call to action may also be identified within C-Path consortia through landscape analysis of literature, clinical trials, and available clinical study data. The unmet need is further developed and refined iteratively by C-Path consortia and programs to generate a regulatory strategy defined in regulatory science terminology (terminology in regulatory science refers to the specific language, terms, and definitions used to

describe concepts, processes, and standards related to the regulation of medical products like drugs, medical devices, and biologics. This terminology ensures clear communication among stakeholders, including regulators, industry professionals, and researchers, facilitating a common understanding of regulatory requirements and practices).[10,11] As a neutral convener, C-Path aims to address unmet needs through the creation and advancement of DDTs and by making DDTs available to a wide range of stakeholders. The unmet need identification process should include the involvement of all relevant stakeholder groups (i.e., patients, academic and clinician researchers, industry, and regulatory bodies) and their respective perspectives to ascertain whether this unmet need resonates across groups and not just within one stakeholder segment.

If this process does not reflect the input and alignment of all stakeholder groups or, if no unmet need is identified, groups run the risk of wasting valuable resources in an endeavor that may not lead to a regulatory-ready solution. For example, a consortium of academic researchers had been working on imaging approaches for coronary arteries. The FDA referred the academic researchers to C-Path, and we encouraged them to get industry representation, in order to bridge the translational science gap to bring a novel idea to the market for patient access. The academic consortium eventually got two companies to join the conversation, and C-Path prompted the two companies to provide their perspectives on whether the coronary artery imaging techniques being proposed by the academic consortium would address an unmet need of drugs in the company's pipeline. C-Path asked, "What are your unmet needs, and can these unmet needs be solved by imaging the coronaries?" There was not a tangible answer at the time. C-Path advised the academic researchers to have stronger involvement from industry in the dialogue, to articulate an unmet need in proper regulatory science terminology and a properly envisioned COU. C-Path's guidance and focus on defining the unmet need prevented the consortium from sinking valuable time into an effort that, while novel, did not yet solve an unmet need in drug development.

2.2 DEFINING THE CONTEXT OF USE

An intended application defines the scope of use for the DDT and defines the quality and quantity of evidence needed to support the DDT's use. In the case of a DDT being considered in a formal FDA or EMA regulatory pathway, the intended application is its COU and further defines the target population, the stage of drug development for use, and what is out-of-scope for its COU. The COU should reflect

terminology from both the Biomarkers, EndpointS, and other Tools (BEST) glossary and the tool's specific use in drug development.[12] The COU may evolve over time dependent on the understanding of the level of evidence or data needed to support it, and as new evidence is being generated. Additionally, formal and informal meetings with the FDA and/or EMA may result in changes or refinements to the COU throughout the regulatory endorsement process. Each case example below will further discuss the importance of the COU and how the COU was developed.

2.3 DEVELOPING SUPPORTING EVIDENCE

The process of evidence generation and validation for novel DDTs requires a comprehensive, multi-faceted approach that combines rigorous testing and real-world clinical validation. Evidence generation strategies should be tailored to the unique tool and its intended use. For biomarkers, evidence generation involves establishing analytical validity through non-clinical studies that demonstrate accuracy, precision, and reproducibility, followed by clinical validation studies to link the biomarker to specific biological processes or clinical outcomes. COAs require evidence to demonstrate their reliability, validity, and ability to detect meaningful changes in patients' disease condition and are often gathered through qualitative research with patients, cognitive interviews, and psychometric validation studies. For trial simulation tools, such as modeling and simulation approaches, evidence is needed that supports their predictive accuracy and reliability and is often generated through retrospective validation using existing trial data and prospective testing of model predictions against real-world outcomes. For these tools, evidence generation should include assessment of their performance across a diverse population of patients, disease states, and clinical settings to ensure their broad applicability and to identify certain limitations. Such a comprehensive approach can ensure that DDTs are supported by appropriate evidence that meets regulatory standards and confirms their utility in drug development.

Efficient data sharing and unified data standards are essential to directly inform and streamline the regulatory path for evidence generation and medical product development. Leveraging its neutral status and elite data competencies, C-Path has ingested and aggregated diverse types of patient-level data across its consortia and programs, including preclinical and clinical, registries, natural history, imaging, digital and real-world data that may be generated from electronic health records (EHRs), patient surveys and health claims. Such data initiatives are highly resource intensive, and careful attention to data sufficiency inflection points is essential and necessitates early and often engagement with stakeholders

and regulators. Depending on the underlying data type and the COU for the DDT in question, the data undergoes bespoke curation, standardization, ontology mapping, and analyses to optimally and iteratively support evidence generation and regulatory decision-making.

2.4 DEVELOPING A REGULATORY SCIENCE-BASED SOLUTION AND REGULATORY STRATEGY

The process of identifying a regulatory science-based drug development solution for a well-defined unmet need begins with feasibility assessment to determine sustainability of a consortium or working group that is comprised of members from regulatory authorities, pharmaceutical industry, academia, non-profits, and patient groups. A broad scope analysis to understand the current state and landscape of the unmet need(s) and identify potential DDTs is employed along with literature review and identification of available patient-level data sources in support of those solutions. Potential DDTs undergo iterations of feasibility assessments to refine the solutions. This process continues until a regulatory science-based solution is developed that addresses a clearly defined unmet need, supported by existing patient-level data or data that can be collected prospectively through future studies. After a DDT is sufficiently refined, a project plan to fully validate and seek appropriate regulatory endorsement of the solution is developed and work to complete the tool begins.

A final regulatory strategy is reliant on the unmet need, the COU, the identified solution, and the totality of evidence obtained and generated. It is essential to understand the regulatory landscape and whether there is precedent for the use of formal or informal pathways for regulatory endorsement. For example, surrogate endpoint qualification is a high bar requiring significant data to show that the endpoint is able to predict clinical benefit and has a clear mechanistic rationale. If the appropriate data do not yet exist or cannot be obtained to support the qualification of a biomarker as a surrogate endpoint, an alternative regulatory pathway may be pursued such as formal biomarker qualification for a different biomarker category. Early and frequent conversations with regulatory authorities take place to align on the ideal regulatory strategy.

CHAPTER 3: THE FRAMEWORK IN ACTION

To demonstrate the application of this Regulatory Science Framework for Drug Development, five case studies are presented below. These case studies vary in disease and DDT types, and all follow the

developmental Framework. Each case example demonstrates how the unmet need was identified, how the supporting evidence was collected, and how collaboration yielded a regulatory-grade solution based on a regulatory strategy.

3.1 TOTAL KIDNEY VOLUME AS A PROGNOSTIC BIOMARKER

3.1.1 DEVELOPING AN EVIDENTIARY FRAMEWORK (TKV)

Unmet Need

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a debilitating genetic disease affecting more than 600,000 individuals. With only one drug approved as of 2024, there is a need for improved therapy due to side effects experienced and earlier intervention. ADPKD poses challenging clinical disease designs, and there is an urgent need to better identify "optimal" clinical trial participants. The PKD Foundation and industry groups approached C-Path to assist in identifying the unmet need and developing regulatory-grade evidence for a biomarker that assesses disease progression at an earlier disease stage when patients are more likely to respond to new therapies and before patients have incurred serious, irreversible kidney damage.

Solution & Supporting Evidence

The initiative to develop a regulatory-grade solution for ADPKD began as an interaction between the PKD Foundation and the FDA in 2007 to facilitate clinical trial development of ADPKD therapies through the qualification of total kidney volume (TKV) as a measure of disease progression. On July 17, 2007, FDA and PKD Foundation held a public workshop entitled "Clinical Trial Endpoints in Polycystic Kidney Disease." Workshop participants found that kidney/cyst growth as a primary outcome may be a target worth exploring in PKD drug development. In a follow-up meeting in March 2008, a recommendation by FDA to create a PKD clinical database to aggregate data across registries and clinical trials to support development of CTS tools to detect disease progression and/or measure symptom relief in PKD patients. These early efforts led to a teleconference in January of 2009 with participants including clinicians and scientists with PKD expertise, FDA, the National Institutes of Health (NIH), Clinical Data Interchange Standards Consortium (CDISC), C-Path, and the pharmaceutical industry to provide an overview of the PKD Foundation and CDISC, gauge interest in a collaborative effort to move this process forward, and discuss funding of the Consortium and next steps.

Next steps included creating a clinical database to aggregate data to support new DDTs. It was recognized early in this process that registries containing long-term results of patients with TKV measurements were not standardized, i.e., data had been collected in different formats, with different definitions. A face-to-face meeting was held in August 2009 with CDISC, FDA, C-Path, the PKD Foundation and industry members to address creating a CDISC Study Data Tabulation Model (SDTM) standard for the common ADPKD data elements and provide the basis for mapping legacy and prospective data. Developing the SDTM data standard involved reconciling five sets of case report forms containing more than 1,200 individual data elements. This process took about a year and required 3 face-to-face meetings and multiple conference calls.

Once the draft data standard had been developed, C-Path officially launched PKDOC on July 15, 2010, consisting of members from the PKD Foundation, Tufts University, Mayo Clinic, Emory University, University of Colorado, Otsuka, Pfizer, Novartis, Amgen, Roche, and Genzyme. In August 2010, PKDOC held a face-to-face workshop to prioritize the ADPKD data elements and discuss possible qualification outcomes. Over the next year, the ADPKD patient registry data from three academic research institutions and from the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) observational study were mapped to the standard by programmers at the academic institutions with assistance and training from C-Path and CDISC. Since that time, C-Path has developed a dedicated Data Collaboration Center (DCC) to provide large scale data solutions for scientific research. DCC now provides hands-on expertise in planning and execution of multisource data standardization, management and aggregation, shortening the time to complete this process.

Using the aggregated, shared data, a disease model was developed that evaluated the relationship between baseline TKV and progression of ADPKD. The modeling, done in conjunction with the PKD Foundation, academic, industry and regulatory stakeholders, was used to support the regulatory qualification of baseline TKV as an enrichment prognostic biomarker of ADPKD and was submitted to the FDA and EMA's respective qualification pathways. A Letter of Support (LOS) was issued from the FDA on March 23, 2015, followed by the Final Guidance for Industry on September 21, 2016. The EMA issued a final Qualification Opinion on October 23, 2015.[13,14]

Following the call to action, stakeholders initially wanted TKV to be qualified as a surrogate endpoint. Discussions with the FDA led to the acknowledgement that the clinical trial data necessary to support surrogacy was not available; however, registry and observational study data were available to support a

prognostic biomarker for trial enrichment. From this experience, early and often engagement with regulatory authorities was crucial for the development of the COU and for the success of TKV biomarker qualification.

3.1.2 THE DIRECT IMPACT (TKV)

As an accelerator, PKDOC's contributions have enhanced the ADPKD drug development process. TKV was accepted as a prognostic biomarker on the basis of approval for JYNARQUE® (tolvaptan) in 2018, the first treatment to slow kidney function decline in adults at risk of rapidly progressing for ADPKD.[15] The collaborative construct provided through C-Path's consortia has led to a generation of actionable solutions that enable the positive transformation of the drug development process. As a result, patients have access to better and safer drugs earlier than they otherwise would.

With use of data from the tolvaptan approval in combination with models used to support the qualification of TKV as a prognostic biomarker, the FDA designated TKV as a reasonably likely surrogate endpoint,[1613] which has helped to stimulate a robust ADPKD drug development pipeline that now includes more than 10 drug candidates under evaluation from preclinical to the late clinical stages of testing. Additionally, the use of TKV as a primary endpoint in the STAGED-PKD trial allowed for the study to end early due to futility following analysis of rate of change in TKV in patients receiving Venglustat compared to placebo, tangibly reducing patient burden by not administering an ineffective treatment.[16,17]

PKDOC continues to generate solutions that further accelerate ADPKD drug development. Current projects in PKDOC are focused on the development of a CTS tool for ADPKD, identification and qualification of novel prognostic and drug response biomarkers, and development of COA/patient-reported outcome (PRO) tools.

3.2 ISLET AUTOANTIBODIES AS A PROGNOSTIC BIOMARKER

3.2.1 DEVELOPING AN EVIDENTIARY FRAMEWORK (ISLET AA)

Unmet Need

Type 1 diabetes (T1D) is an autoimmune disease resulting in the destruction of pancreatic insulin-producing beta cells. The staging classification for T1D established three distinct stages of disease. Stage 1 represents the presence of two or more islet autoantibodies (AAs) in patients who are normoglycemic. Stage 2 represents the presence of two or more islet AAs and dysglycemia. Stage 3 represents the clinical manifestation of T1D and the onset of symptoms of disease. There is a growing unmet medical need for therapies that target the underlying disease process and progression. At the start of this work, there were no approved disease-modifying drugs for T1D. A major challenge in T1D drug development is the considerable variability among patients and the wide range of disease progression rates, which makes it difficult to identify optimal patient populations. Pharmaceutical industry members approached C-Path with an unmet need and call to action to identify a tool to optimize the identification of individuals who are likely to rapidly progress to stage 3 disease during clinical trials.

Solution & Supporting Evidence

In 2017, C-Path's Type 1 Diabetes Consortium (T1DC) was founded as a PPP between stakeholders from the pharmaceutical industry, patient advocacy groups, philanthropic organizations, clinical research groups, the National Institute of Health (NIH), and the FDA. Work began to define the existing unmet need, potential regulatory science solutions, and patient level data sources to inform consortium activities. The consortium identified islet AAs as a potential prognostic biomarker for clinical trial enrichment.

The T1DC aimed to develop a regulatory-grade model that could accurately identify individuals likely to progress to stage 3 T1D during trials of reasonable duration while incorporating important sources of patient heterogeneity, including sex, age, and glycemic status, with islet AA status. In May 2019, T1DC sought qualification advice from the EMA. During the qualification advice procedure, the EMA issued a LOS for T1DC's work and encouraged the T1D community to get involved by means of collaboration and data sharing in order to permit timely and robust development and validation of the model. The EMA also provided feedback on the available data and the proposed analysis.

The T1D community and researcher engagement served as a facilitator for the sharing of data to better understand disease progression. Following receipt of the EMA LOS, the T1D community stepped up and shared more data that were integrated into the existing T1D database. The T1DC received, curated, and aggregated data from three longitudinal studies: The Environmental Determinants of Diabetes in the Young (TEDDY) study, the TrialNet Pathway to Prevention (TN01), and the Diabetes Autoimmunity Study in the Young (DAISY). As per the feedback received from the EMA during the qualification advice process, the modelling dataset included data from TEDDY and TN01, with data from DAISY used for external validation. A literature review on past modeling efforts was used to guide the analysis needed to support the use of islet AAs in clinical trial decision making. The modelling analysis was discussed with the EMA at several points throughout the qualification process and is described thoroughly in the T1DC's regulatory submissions.

In July 2020, T1DC submitted their briefing dossier for a full qualification opinion to the EMA. In March 2022, the EMA's Committee for Medicinal Products for Human Use (CHMP) concluded that the evidence from the modelling exercise was sufficient and supportive of the stated COU, and issued a positive qualification opinion on March 24, 2022, for the use of islet AAs as enrichment biomarkers in T1D prevention clinical trials.[18]

3.2.2 THE DIRECT IMPACT (ISLET AA)

Following the EMA qualification in July 2022, T1DC published "Consortium-based approach to receiving an EMA qualification opinion on the use of islet AAs as enrichment biomarkers in type 1 diabetes clinical studies" in Diabetologia and developed a publicly available Islet Autoantibody Clinical Trial Enrichment Tool.[19,20] In November 2022, a T1DC consortium member, Provention Bio's Teplizumab received FDA approval as the first treatment to delay onset of clinical stage 3 T1D. Later in December 2022, a letter to the editor from the FDA was published in Diabetologia entitled, "Utility of islet autoantibodies as enrichment biomarkers in type 1 diabetes clinical studies: a viewpoint from the FDA," which also helped inform stakeholders of the intended application of the biomarkers in drug development.[21]

The qualification of islet AAs as a prognostic biomarker serves as the first regulatory-endorsed approach to clinical trial enrichment in T1D. The models are publicly available and allow individual risk assessment during study screening to identify individuals who are eligible for participation and provide drug developers with a higher level of confidence that their trials are enriched in a manner consistent with

regulatory agency thinking. Additionally, this qualification serves as a foundation for the use of prognostic biomarkers for prevention trials in other indications.

3.3 FRIEDREICH'S ATAXIANATURAL HISTORY DATA AS A PART OF THE TOTALITY OF EVIDENCE

3.3.1 DEVELOPING AN EVIDENTIARY FRAMEWORK (FA)

Unmet Need

Friedreich's Ataxia (FA) is a rare autosomal recessive neurodegenerative disease characterized by gait and limb ataxia, dysarthria, loss of reflexes, proprioceptive dysfunction, and muscle weakness, as well as non-neurological features including cardiomyopathy, diabetes, and scoliosis. Finding treatments able to slow down or halt FA disease progression and design optimal trials to determine efficacy and safety remains an area of significant unmet need. In 2018, the Friedreich's Ataxia Research Alliance (FARA) came to C-Path with this unmet need and a request to collaborate on a clinical database to collate FA data.

Solution & Supporting Evidence

The database was constructed to include aggregated data standardized to CDISC to ensure regulatory submission readiness and to serve as an open resource for industry members, academia, and other stakeholders to access. Exemplary of its long history of expertise in data standards development, curation, and oversight of multiple data-sharing initiatives, C-Path executed data sharing agreements, accumulated the data, and standardized the data to CDISC.

Launched in February 2019, the Friedreich's Ataxia Integrated Clinical Database (FA-ICD) was designed to catalyze and accelerate FA research and drug development by curating and standardizing FA clinical trial and natural history data into CDISC format and making this data publicly available to qualified researchers. These researchers can access and analyze data in aggregate, or filter and view individual de-identified patient-level data from four clinical trials and a large FA natural history study (FA-COMS).

Since its launch, the FA-ICD has received numerous inbound access requests to explore the database and, in a mechanism distinct from its other formal consortium infrastructure, C-Path has established task forces to explore the data and identify potential new regulatory-grade DDTs. One such use case is

referenced in the approval of Reata Pharmaceutical's (now Biogen) omaveloxolone (SKYCLARYS) for FA in February 2023.[22] Upon completion of a phase II trial, the data demonstrated a statistically significant difference between omaveloxolone and control arm based on modified FA rating scale (mFARS) scores. However, there was a question of whether this difference constituted evidence of benefit. The FDA and Reata held formal meetings in December 2019 and August 2020 discussing this result.[23] Both parties were aware of the FA data available in the FA-ICD, and the team at Reata, in collaboration with statisticians at FARA and WCG-Statistics Collaborative, performed a post-hoc propensity match-based analysis using patient data from the FA-COMS longitudinal study and Reata's MOXIe extension trial to demonstrate that omaveloxolone provided a persistent benefit over 3 years out compared to the matched participants from the FA-COMS study.[23,24] This bespoke use of the FA-ICD provided a unique opportunity for an industry stakeholder to access and analyze data needed for a propensity-matched analysis to contribute to the totality of evidence in the approval of omaveloxolone for patients with FA.

3.3.2 THE DIRECT IMPACT (FA)

In addition to external stakeholder uses, use of the FA database by C-Path task forces has led to a recent Letter of Intent (LOI) submission under the Fit-for-Purpose initiative for a modeling-based CTS tool focused on the dynamics of change of the mFARS to optimize trial design in FA. As of September 2024, this LOI is under review by FDA via the Fit-For-Purpose initiative.

Learnings from the development of the FA-ICD have informed the development of the Rare Disease Cures Accelerator-Data and Analytics Platform (RDCA-DAP) and the FA-ICD is now hosted on RDCA-DAP. The use of external controls in a propensity match-based analysis demonstrates the successful development and use of a data platform, the execution of data sharing, and the standardization of regulatory-grade data. C-Path's RDCA-DAP provides a centralized and standardized infrastructure to support and accelerate rare disease characterization targeted for clinical development. Additionally, the platform advances best practices to help enhance future data collections, including natural history studies, with attention to established data quality standards, in order to be most useful to clinical trial design and regulatory review.

3.4 THE MYELOFIBROSIS SYMPTOM ASSESSMENT FORM V4.0 AS A PRO MEASURE TO ASSESS MYELOFIBROSIS SYMPTOMS

3.4.1 DEVELOPING AN EVIDENTIARY FRAMEWORK (MFSAF)

Unmet Need

Myelofibrosis (MF) is a rare bone marrow cancer that impairs the body's ability to produce normal blood cells. As a result, excessive scarring (fibrosis) forms in the bone marrow, and a cardinal sign is an enlarged spleen (splenomegaly). People with MF may suffer from symptoms that include fatigue, abdominal discomfort, bone pain, night sweats, itching, and early satiety. Improvement of symptoms is an important goal of clinical trials. However, numerous variable questionnaires were being used across trials to assess symptoms in MF drug development programs, all stemming from the original Myelofibrosis Symptom Assessment Form (MFSAF). The FDA recognized the regulatory uncertainty due to lack of harmonization and approached C-Path with an unmet need to harmonize the MFSAF.

Solution & Supporting Evidence

In 2016, C-Path's PRO Consortium established an MF Working Group to create a publicly available, consensus-based, harmonized version of an MF symptom questionnaire that can be used in MF treatment trials. After finalizing the questionnaire, the working group would facilitate its adoption across industry and academia. The MF Working Group focused on seven symptoms: fatigue, night sweats, pruritus, abdominal discomfort, pain under ribs on the left side of the body, early satiety, and bone pain. Initial steps included completing a literature review of all existing variations of the MFSAF to identify items related to the seven core MF symptoms.

The Working Group's harmonization panel meeting was held in March 2016. The harmonization panel included an MF patient, representatives from the C-Path, the FDA, and pharmaceutical companies, as well as clinical experts and individuals with expertise in the development of Patient-Reported Outcome (PRO) questionnaires for use in clinical trials. Recall interval and mode of administration were discussed. Each symptom item was discussed, and the MF Working Group considered how to word the instructions, item text, and response options until a consensus was achieved. The harmonized instrument was named the MFSAF v4.0 and is the latest "official" version of this PRO measure.[25]

3.4.2 THE DIRECT IMPACT (MFSAF)

Multiple versions of symptom assessment questionnaires have been used in MF drug development programs. The MF Working Group created a single harmonized, consensus-defined symptom assessment questionnaire, the MFSAF v4.0, based on available empirical evidence. It can be used as an endpoint measure in MF treatment trials to assess clinical benefit. Further information about the MFSAF v4.0 and how to license it is available at: https://www.c-pathcoas.org.[26]

In addition to its public availability, the MFSAF v4.0 is now listed in FDA's COA compendium as a measure of MF symptom severity in trials of patients with intermediate or high-risk MF, post polycythemia-vera MF and post essential thrombocythemia MF who are symptomatic.[27] The MFSAF v4.0 has now been licensed for use in clinical trials over 50 times, with most new trials using this consolidated version of the MFSAF.

Lastly, the consensus work completed by the MF Working Group is an example of the development of a regulatory-grade PRO that has been widely adopted for use using an informal regulatory strategy rather than pursuing the formal FDA qualification pathway.

3.5 ALPHA SYNUCLEIN SEED AMPLIFICATION ASSAY AS A SUSCEPTIBILITY/RISK BIOMARKER

3.5.1 DEVELOPING AN EVIDENTIARY FRAMEWORK (A-SYN SAA)

Unmet Need

Synucleinopathies are a group of neurodegenerative disorders, including Parkinson's disease (PD) and Dementia with Lewy Bodies (DLB), that are characterized by a shared feature of aggregation of alpha synuclein (α-syn) in cytoplasmic inclusion bodies in cells of the affected brain regions. There are limited treatments available for synucleinopathies, and the only regulatory approved therapies focus on the treatment of motor symptoms after clinical presentation. There is an urgent need for disease-targeted treatments that can halt, reverse or prevent disease progression. Two factors interfering with development of disease-targeted treatments are challenges in accurate diagnosis of synucleinopathies and the need to intervene earlier in the progression of the disease.[28,29] Data show that at the time of onset of motor symptoms of PD and patient diagnosis, significant neurodegeneration has already occurred.[30–32] Additionally, current diagnosis relies on clinical signs and symptoms. Development of

biomarkers for synucleinopathies may accelerate an earlier, accurate diagnosis before significant neurodegeneration occurs and enable clinical trials focused on earlier disease stages. The Critical Path for Parkinson's (CPP) consortium is focused on advancing drug development tools aimed at early intervention. In doing so, CPP has facilitated a call to action and established the Biofluid Biomarker Working Group, comprised of industry members, non-profit organizations such as The Michael J. Fox Foundation for Parkinson's Research (MJFF) and Parkinson's UK, FDA and the National Institute of Neurological Disorders and Stroke.

Solution & Supporting Evidence

In April 2023, CPP co-organized a virtual symposium called the 2023 PD Staging Roundtable to discuss a new biological staging framework. Participants included representatives from the EMA, FDA, and the United Kingdom's Medicines and Healthcare products Regulatory Agency. A Position Paper was published by roundtable representatives establishing a novel biological staging framework called the neuronal α-syn integrated staging system (NSD-ISS) based on innovative advances in biomarkers and genetics.[33] This biological definition is based on the presence of α-syn pathology and the framework follows the precedent of the Huntington's Disease integrated staging framework (HD-ISS) facilitated by C-Path's HD-RSC consortium.[34]

The CPP Biofluid Biomarker Working Group conducted a literature review of the field of α-syn measurements across a range of target populations in various biofluids and tissue compartments. The literature review enabled refinement of a long list of candidate biomarkers to select an α-syn seed amplification assay (SAA) as the priority biomarker for near-term focus. Previously, the traditional standard for identification of pathogenic α-syn protein occurred during postmortem evaluation. Recent innovation of the α-syn SAA technique has allowed for detection and measurement of α-syn aggregates in human cerebrospinal fluid (CSF). Due to an initiative led by MJFF to harmonize and validate the assay, α-syn SAA has been increasingly implemented in clinical trials and observational studies.

Building from this foundation, the CPP Biofluid Biomarker Working Group comprehensively evaluated data from five observational studies derived from geographically diverse populations and from two randomized controlled clinical trials targeting α-syn. The observational studies included the MJFF Parkinson's Progression Markers Initiative (PPMI), a landmark longitudinal natural history study with data from PD patients, healthy volunteers and individuals at risk of developing Parkinson's disease. The study assessed changes in biomarkers at different stages of disease and evaluated whether the a-syn

SAA test reliably and reproducibly measured and distinguished PD from controls and had the potential to detect PD in patients before the onset of motor symptoms. The results demonstrated that CSF α-syn-SAA has high diagnostic utility as a biomarker in individuals diagnosed with PD, DLB and Random Eye Movement (REM) Sleep Behavior Disorder and demonstrated a high level of sensitivity and specificity.

A series of meetings with FDA that included CDER's Office of Neuroscience (ON) staff took place from October 2022 to January 2024 aimed at reviewing the relevant data, aligning diverse stakeholders in the field to discuss opportunities for future validation and confirming the role of α-syn SAA in supporting ongoing and future clinical trials. The advancement of the NSD-ISS framework in parallel with the CPP biomarker effort for α-syn SAA served to align further with FDA as staff from the FDA Office of Neuroscience were coauthors of the NSD-ISS manuscript published in Lancet in Jan 2024.[33] These early-and-often informal regulatory interactions culminated with the submission of a Letter of Support (LOS) request to the FDA on May 1, 2024.

3.5.2 THE DIRECT IMPACT (A-SYN SAA)

On August 19, 2024, the FDA issued an Letter of Support (LOS) in a record time of less than four months.[35] The issuance of an LOS for the α-syn SAA has had far reaching implications and anecdotally, through conversations among consortia members, there has been an increase in both data sharing and the use of the biomarker in clinical trials and observational studies. The LOS encouraged the further use and study of α-syn SAA as a susceptibility/risk biomarker for enrichment of clinical trials in PD and related synucleinopathies. Additionally, the FDA highlighted the open sharing of data used in the LOS request and encouraged further data sharing to enable confidence in the use of this biomarker.[35]

MJFF recently funded 15 clinical research cohort studies from targeted populations that will all apply the α-syn SAA, and investigators have agreed to share the data from their studies as part of the MJFF funding agreement.[36] A publication highlighting the role of open science and data sharing in paving this path is in press.[37]

In addition, the α-syn SAA biomarker is being applied in an innovative platform clinical trial entitled the Path to Prevention Therapeutics platform trial.[38] This will be the first ever platform trial to be conducted in at-risk PD participants prior to onset of clinical symptoms. Moreover, the α-syn SAA is now being evaluated in Alzheimer's disease observational studies[39,40] and RCTs.[41]

3.6 HOLLOW FIBER SYSTEM OF TUBERCULOSIS (HFS-TB) AS A PRECLINICAL MODEL TO EVALUATE DOSING REQUIREMENTS FOR TB DRUGS

3.6.1 DEVELOPING AN EVIDENTIARY FRAMEWORK (HFS-TB)

Unmet Need

Tuberculosis (TB) is a public health epidemic, particularly affecting developing countries, with more than 10 million cases being reported globally by the World Health Organization in 2021.[42] In 2010, the Critical Path to Drug TB Regimens (CPTR) Initiative was launched to develop new methods and tools in the development of promising TB drug candidate combinations. CPTR was formed through the collaboration and support of the Bill & Melinda Gates Foundation, the Global Alliance for TB Drug Development and the Critical Path Institute. At the time of CPTR's launch, it had been 40 years since a new drug was available to treat TB.[43] Concurrently, multi-drug resistant Myobacterium TB (Mtb) was on the rise and posed a significant challenge to develop novel and effective treatments for TB. There was a serious unmet need to accurately and efficiently rank-order combinations of existing TB drugs to fight Mtb.

Solution & Supporting Evidence

Animal models have historically been the preferred model in TB drug development; however, there were issues with the accuracy of clinical efficacy predictability, the limited use in assessment of acquired drug resistance in combination regimens, and the lack of repetitive sampling needed for extrapolation of models to time-to-event outcomes.[44] In 2004, Gumbo et al. published a novel *in vitro* pharmacodynamic infection model of TB called the hollow fiber system of TB (HFS-TB).[45] The HFS-TB model was refined over time and identified by CPTR as a potential preclinical efficacy model to evaluate TB drug combinations.

CPTR conducted a landscape analysis to identify publications including 1) all HFS-TB studies published between 2000-2012, including Monte Carlo simulations; 2) clinical studies for TB drugs published prior to HFS-TB studies; and 3) clinical studies published at least 6 months after the HFS-TB publication. Data obtained across the literature searches were compared, and clinical study data were analyzed for correlational and predictive accuracy of HFS-TB. The results demonstrated a validated predictive accuracy of HFS-TB and supported its use as a tool for TB drug dose selection and regimen design.[44]

Discussions with regulatory authorities were initiated early in the process. CPTR initially submitted an LOI to the FDA in February 2013, followed by a teleconference at the end of the month. An analysis plan

was agreed upon, and CPTR followed a Voluntary Exploratory Data Submission (VXDS; program no longer available) process with the FDA in October 2013. Following a VXDS meeting in November 2013, the FDA encouraged the CPTR team to submit comments to the docket for the guidance document on TB drug development. Additionally, the FDA suggested co-publication in peer-reviewed journals.[46]

CPTR pursued a formal Qualification Opinion mechanism with the EMA's CHMP. A qualification opinion rather than qualification advice was requested based on the robust data and analyses supporting the HFS-TB model and informal conversations with EMA around the benefits of this model. CPTR submitted a briefing document in February 2014. In May, a Scientific Advice Working Party (SAWP) meeting was held in which results were thoroughly discussed, with the SAWP making a recommendation to the CHMP that a positive qualification opinion be issued. In November 2014, the EMA issued a draft qualification opinion.[47]

3.6.2 THE DIRECT IMPACT (HFS-TB)

The EMA qualification opinion was finalized and published in January 2015. The FDA published an editorial in *Clinical Infectious Diseases* in August 2015 recognizing the work of CPTR, as well as encouraging use of the HFS-TB and further scientific advancement in approaches to identifying drug regiments to increase clinical trial efficiency.[48]

The impact of the HFS-TB qualification is twofold – 1) revitalization of the TB drug regimen development pipeline by streamlining the development of new TB drugs and drug combination treatments and 2) providing a model-based analysis of previous TB trials to inform and improve future trial design. Thus, the HFS-TB qualification provides a regulatory framework that supports the design and interpretation of TB preclinical studies. After more than 40 years of stagnation, patients around the globe have the first new drug regimens for TB, as well as a drug regimen development pipeline to meet the needs of TB patients everywhere.

Since its qualification, the HFS-TB has been documented in several case studies[49] including use in non-TB indications.[50] Drug developers now have additional tools available to reduce combinations and exposures before animal and human studies, helping decide which drugs to pair and at what doses, especially for multi-drug regimens for drug-resistant TB. The increased use of the HFS-TB highlights its significant role in developing TB treatment regimens, guiding clinical trial design, and influencing public health policy in TB programs.[51,52]

The HFS-TB also serves as an example of the first qualified new approach methodology (NAM) by the EMA. NAMs serve to assess the safety, efficacy, and quality of medicinal products while replacing, reducing, or refining (3Rs) the use of animals. The HFS-TB has distinct advantages over in vivo animal models such as the capacity to simulate human pharmacokinetic/pharmacodynamic (PK/PD) of a drug or drug combination, ability to determine bactericidal and sterilizing effect rates and the likelihood of resistance emergence, repetitive sampling, and assessment of drug combinations.

CHAPTER 4: SCALABILITY AND FUTURE USE OF THE FRAMEWORK TO ACCELERATE DRUG DEVELOPMENT

4.1 FUTURE USE AND ADOPTION

The Framework may have far-reaching implications and future use in cases of unmet need. While the case studies highlighted DDTs that were developed with specific COUs, the learnings presented here may be extrapolated and applied to additional areas of need. These areas of unmet medical need included ALS and other rare neurodegenerative diseases, as well as new innovations and technologies such as digital health technologies (DHTs), AI, the use of RWE, and cell and gene therapies.

4.1.1 AMYOTROPHIC LATERAL SCLEROSIS

As evidenced by the enactment of the "Accelerating Access to Critical Therapies for ALS Act" (ACT for ALS) in 2021 and the subsequent selection of C-Path by the FDA and NIH to convene a new PPP, the Critical Path for Rare Neurodegenerative Diseases (CP-RND) in September 2022, efforts are ongoing to articulate and address specific unmet needs for innovative and accelerated development of safe and effective therapies for ALS.

Amyotrophic lateral sclerosis (ALS) is a rare, chronic, progressive neurodegenerative disease characterized by muscle weakness, twitching, and atrophy culminating in loss of voluntary muscle control. The etiology of ALS is not fully understood but involves complex gene-environment interactions. In April 2023, the FDA approved QALSODY (tofersen), an antisense oligonucleotide (ASO)-based therapy for superoxide dismutase 1 (SOD-1) ALS via the Accelerated Approval mechanism based on the fluid biomarker neurofilament light chain (NfL) as a reasonably likely surrogate endpoint.[53] However, the subpopulation of SOD-1 ALS is a minority fraction of total ALS cases, thus the unmet need for improved ALS therapeutics persists. In aggregate, ALS is a heterogeneous disease with variable progression rates.

Through the CP-RND, C-Path is collaborating with relevant stakeholders to address persistent bottlenecks in ALS drug development. By applying the Framework as outlined here, learnings from other regulatory successes have the potential to advance drug development for patients living with ALS, including (1) biomarker development and validation (i.e., potential application of NfL as a biomarker for non-genetic ALS), (2) validation of ALS-specific outcome assessment tools such as functional rating scales, PRO measures, and other assessment tools, (3) optimization of clinical trials with use of innovative trial design, patient stratification modeling, historical control data, and adaptive trial design approaches, (4) disease progression modeling with use of natural history data and predictive modeling, and (5) patient-focused drug development approaches with use of remote monitoring, DHTs, and patient preference studies. With use of the decision tree (Appendix 3), PPPs such as CP-RND can better evaluate incoming calls to action from stakeholders to prioritize efforts that are most likely to yield regulatory-grade solutions.

4.1.2 OTHER FUTURE USE CASES

Another example of current and scaling application of the Framework focuses on lysosomal disorders (LDs). After the initial outreach from FDA to help consolidate current clinical and research understanding of more than 70 types of lysosomal disorders, C-Path embarked on a pre-consortium assessment exercise to determine the sustainability of a consortium to address critical unmet needs for LD. In 2023, the Critical Path for Lysosomal Diseases (CPLD) consortium was established, dedicated to forging a dynamic PPP aimed at accelerating DDT development for those impacted by LDs. The consortium efforts are focused on LDs as a disease family not on individual LDs. CPLD has engaged diverse stakeholders to convene the experts in the LD space, has conducted data landscape assessments, and is currently applying the principles of the Framework to identify the unmet need(s) and the candidate solution(s), with concomitant supporting evidence requirements across the family of LDs. NfL serves as an indication of neuronal health in many central nervous system disorders. Once the neuronal membrane or protein secretion is disrupted under disease conditions, NfL is released into the cerebrospinal fluid and can be measured. NfL correlates to disease progression and survival in ALS,[54] to long-term clinical outcomes in multiple sclerosis (MS),[55] and to subtypes of LDs.[56,57] The CPLD consortium has established a workgroup to focus on fluidic and neuroimaging biomarkers, including investigating NfL as a potential biofluid biomarker for LD.

The use of DHTs to support novel DDTs is another early-stage example of disease agnostic and/or disease family application of the Framework. Notably, DHT-derived DDTs are unique in the sense that

the final tool can have multiple applications, like a biomarker or a COA, depending on the specific COU and supporting evidence. C-Path is coordinating stakeholder engagement and developing regulatory science strategy for DHT development using this Framework, across several consortia/programs, including neuroscience (Critical Path to Parkinson's, CPP), rare neurodegenerative diseases (CP-RND-ALS and Huntington's Disease Regulatory Science Consortium, HD-RSC), and the COA Program.

A strategy similar to this holistic DHT approach is in development for applying the Framework to AI initiatives and for cell and gene therapies in neonates/pediatric populations, where learnings from previously elucidated case studies (i.e., T1D for early intervention/prevention clinical trials) can be applied to new DDTs.

C-Path's Data Collaboration Center and Quantitative Medicine teams are actively expanding on lessons learned from various C-Path Consortia, including those that focus on neonatal drug development, Parkinson's disease, Alzheimer's disease, and the RDCA-DAP to improve the ingestion, curation, and analysis processes of multiple types of data sources in rare and orphan diseases, including clinical trials, RWD, observational studies, etc. RWD from EHRs and DHTs promise to provide unique insights and promote development of nuanced DDTs. Target trial emulation, trial simulation tools, and digital twins can expand opportunities in the study of rare neurodegenerative conditions including ALS.

4.2 CONCLUSION

The goal of this Framework is to de-risk the development of DDTs through emphasis on collaborative innovation and shared learnings. This Framework is designed to be an essential knowledge management tool to capture learnings from previously developed and validated solutions. Informed by examples of DDTs developed by C-Path and its consortia/task force members, standards and key decisions have been outlined to further reduce uncertainty when developing DDTs and ultimately accelerate drug development. Additionally, this Framework seeks to increase transparency and decrease perceived and actual barriers to participation across C-Path's consortia and working groups.

The Framework can impact stakeholders across the drug development spectrum including but not limited to regulators, people living with insufficiently treated diseases, and representatives from the pharmaceutical industry. The validation of a DDT such as TKV or islet AAs as prognostic biomarkers may build the confidence regulators have in the tools and endpoints used in clinical trials while also providing

a standard that can be consistently used across an indication. Use of the LOS mechanism to demonstrate support in cases such as aggregated α-syn as a susceptibility or risk biomarker for enrichment of clinical trials can catalyze data sharing and the use of the biomarker in clinical trials and observational studies. The qualification of novel models, such as HFS-TB, may offer new insight into drug development for conditions with a high burden globally and at risk for treatment resistance, while also serving to replace, reduce or refine the use of animals in drug development. Additionally, the accelerated development of fit-for-purpose DDTs provides people living with diseases endpoints that better capture improvements in how they feel and function as demonstrated by the harmonization of the MFSAF v4.0. Lastly, the accelerated development of DDTs with use of the Framework serves to derisk drug development for industry through the use of resources such as the RDCA-DAP, which has accelerated the generation of DDTs that have been endorsed by regulatory bodies.

The implementation of a regulatory science framework for DDTs, such as that presented here, has the potential to transform the pharmaceutical industry via multistakeholder collaborations. First, the Framework can significantly accelerate development timelines by providing clearly outlined pathways for tool validation, enabling more efficient study designs, and reducing time-to-market of new therapies. Second, the Framework enhances decision-making capabilities by providing a foundation for the generation of actionable DDTs. This has a direct impact on guiding the standardization and analysis of relevant data, allowing drug developers to make better-informed choices about development strategies and resource allocation and utilization. Third, the Framework offers substantial cost and time reduction by optimizing trial design to minimize trial failures and reducing redundant testing across the industry. Fourth, the Framework facilitates innovation adoption by encouraging collaboration, creating clear pathways for implementing novel technologies, and generating solutions that all stakeholders can use. Lastly, the Framework leads to improved patient outcomes through more targeted therapies, improved safety assessments, and more relevant endpoints that reflect patient experiences. Taken together, these impacts accelerate technological advancement in drug development while also creating a more efficient, innovative, and patient-centric drug development ecosystem.

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APPENDIX

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2. GLOSSARY OF ABBREVIATIONS AND ACRONYMS

- AAs – Autoantibodies
- ACT for ALS – Accelerating Access to Critical Therapies for ALS Act
- ADPKD –Autosomal Dominant Polycystic Kidney Disease
- AI – Artificial Intelligence
- ALS – Amyotrophic Lateral Sclerosis
- ASO – Antisense Oligonucleotide
- BEST – Biomarkers, EndpointS and other Tools
- CDISC – Clinical Data Interchange Standards Consortium
- CHMP – Committee for Medicinal Products for Human Use
- COA – Clinical Outcome Assessment
- COU – Context of Use
- CPLD – Critical Path for Lysosomal Diseases
- CPP – Critical Path to Parkinson's
- CPIM – Certified in Production and Inventory Management
- CP-RND – Critical Path for Rare Neurodegenerative Diseases
- CRISP – Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease
- CTS – Clinical Trial Simulator
- C-Path – Critical Path Institute
- DAISY – Diabetes Autoimmunity Study in the Young
- DCC – Data Collaboration Center
- DDTs – Drug Development Tools
- DHTs – Digital Health Technologies
- eGFR – Estimated glomerular filtration rate
- EHR – Electronic Health Records
- EMA – European Medicines Agency
- FA – Friedrich's Ataxia
- FA-CID – Friedreich's Ataxia Integrated Clinical Database
- FA-COMS – Friedreich's Ataxia Clinical Outcome Measures
- FARA – Friedreich's Ataxia Research Alliance
- FARS – Focus Areas of Regulatory Science
- FDA – U.S Food and Drug Administration
- HD-RSC – Huntington's Disease Regulatory Science Consortium
- LD – Lysosomal Disorders
- LOI – Letter of Intent
- LOS – Letter of Support
- MF – Myelofibrosis
- mFARS – Modified Friedreich's Ataxia Rating Scale
- MFSAF – Myelofibrosis Symptom Assessment Form
- MIDD – Model-Informed Drug Development
- MS – Multiple Sclerosis

- NfL – neurofilament light chain
- NIH – National Institutes of Health
- PDUFA – Prescription Drug User Fee Act
- PFDD – Patient-Focused Drug Development
- PKDOC - Polycystic Kidney Disease Outcomes Consortium
- PPP – Public-Private Partnership
- PRO – Patient-Reported Outcome
- REM – Random Eye Movement
- RCT – Randomized Controlled Trial
- RDCA-DAP - Rare Disease Cures Accelerator-Data and Analytics Platform
- RWD – Real World Data
- RWE – Real World Evidence
- SDTM – Study Data Tabulation Model
- T1D – Type 1 Diabetes
- T1DC – Type 1 Diabetes Consortium
- TEDDY – The Environmental Determinants of Diabetes in the Young
- TKV – Total Kidney Volume
- TN01 – TrialNet Pathway to Prevention
- VXDS – Voluntary Exploratory Data Submission

3. DRUG DEVELOPMENT TOOL DECISION TREE