# Can Innovative Trial Designs in Orphan Diseases Drive Advancement of Treatments for Common Neurological Diseases?

Diane Stephenson[1,*], Cecile Ollivier[1], Roberta Brinton[2] and Jeffrey Barrett[1]

**Global regulatory agencies have transformed their approach to approvals in their processes for formal review of the safety and efficacy of new drugs. Opportunities for innovation have expanded because of the coronavirus disease 2019 (COVID-19) pandemic. Several regulatory-led initiatives have progressed rapidly during the past year, including patient-focused drug development, model-informed drug development, real-world evidence, and complex innovative trial designs. Collectively, these initiatives have accelerated the rate of approvals. Despite demands to focus on urgent needs imposed by the COVID-19 pandemic, the number of new drug approvals over the past year, particularly for rare diseases, has outpaced expectations. Advancing therapeutics for nervous system disorders requires adaptive strategies that align with rapid developments in the field. Three relentlessly progressive diseases, amyotrophic lateral sclerosis, Duchenne muscular dystrophy, and Parkinson's disease are in urgent need of new treatments. Herein, we propose new regulatory initiatives, including innovative trial designs and patient-focused drug development that accelerate clinical trial conduct while meeting critical regulatory requirements for therapeutic approval.**

Diseases that affect the nervous system comprise an unsustainable burden with exponential rates of growth around the world.[1] Neurodegenerative diseases represent the most relentless of all, as they are universally fatal, affect fundamental functions that impact the quality of life, and are characterized by prolonged periods of disability. With few exceptions, nearly all lack treatments that slow or halt disease progression. The failure rate of clinical trials for neurological disease treatment is one of the highest of all.[2] The global health crisis of the coronavirus disease 2019 (COVID-19) pandemic has resulted in worsened outcomes for those suffering from nervous system diseases.[3,4] The rigorous science-based interventions that have emerged under crisis circumstances, from vaccines to effective drug therapies to population health to governmental policies, have resulted in astounding mobilization across all sectors. These successful endeavors have broader impact beyond COVID and have raised the bar for rapid deployment of disease treatment and lifesaving innovations.

A key contributor to the rapid development and deployment of lifesaving vaccines and treatments in response to the global COVID crisis has been regulatory bodies across the globe. This requires prioritization across the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), the Medicines and Healthcare products Regulatory Agency (MHRA), and the Pharmaceuticals and Medical Devices Agency (PMDA). In the United States, despite unprecedented challenges and focus on COVID vaccines and treatments, the FDA approved a total of 32 novel drugs and biologics with orphan drug designation in 2020.[5] The total number of drug approvals overall was 52, so more than half (58%) were within the rare disease category. This is truly remarkable considering the barriers to success in advancing drugs for approval in rare diseases, including low patient numbers, limited understanding of disease pathology and progression, variability in disease presentation, and a lack of established end points.

The regulatory landscape is clearly a major catalyst for creating paths to drug approvals for rare diseases. A number of innovative platforms, regulatory guidance, and policies have contributed to these orphan drug approval successes. The 1983 Orphan Drug Act incentivized commercial investment in the research and development required to show evidence of the safety and efficacy of treatments is one of them. In just 7 years (1990), the FDA had designated 370 products for orphan status, and of these 49 were approved for orphan indications. Just over a decade later (by 2002) the number of orphan designations grew to almost 1,100, and approvals to 232, a number that provided treatment for an estimated 11 million patients.

Following the successful examples in the United States, in 2000, European Member States adopted the Regulation (EC) No. 141/2000[6] or "the Orphan Regulation" and in 2006 Regulation (EC) No. 1901/2006 "the Pediatric Regulation."[7] As a result, by the end of 2017, 142 new orphan medicines had been authorized in the European Union for 107 unique conditions, including multiple very rare diseases. The number of approved pediatric investigation plans exceeded 1,000 in 2018, of which 450 were completed by June 2018.[8] Despite these remarkable advances, substantial gaps remain in therapies available for rare diseases. It is becoming clear that legislation may act as an enabler, but cannot substitute for the research, development, and manufacturing challenges that affect product development.

[1]Critical Path Institute, Tucson, Arizona, USA; [2]Center for Innovation in Brain Sciences, University of Arizona Health Sciences, Tucson, Arizona, USA.
*Correspondence: Diane Stephenson (dstephenson@c-path.org)

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To complement regulatory and legal incentives, global Health Authorities have recommended the adoption of Innovative Trial Designs to accelerate approvals of safe and effective medicines. Strategies include the use of natural history to generate historical control data for comparison, *in silico* simulations, use of external controls, nontraditional study designs, and identifying inclusion/exclusion criteria and appropriate end points from nontraditional data sources.[9,10] For example, in 2019, the FDA issued draft guidance for industry on Common Issues in Rare Disease Drug Development,[11] and, in 2021, two guidances for developers of antisense oligonucleotide drug products for severe and life-threatening diseases.[12,13]

### Case examples—rare diseases

Two disease areas exemplify where unmet needs are driving novel approaches that have high visibility and broad implications for public health. Both amyotrophic lateral sclerosis (ALS) and Duchenne muscular dystrophy (DMD) are devastating chronic progressive diseases in urgent need of effective therapies. ALS and DMD meet the classification as rare diseases with an incidence of 2 per 100,000 in major Western countries for ALS[14] and 2.8 cases per 100,000 for DMD.[15] Both ALS and DMD are rapidly progressive diseases involving neuromuscular system structure and function. New discoveries, particularly in genetics and biomarkers as well as progress in gene-based therapeutics have catapulted these conditions from the historical perception as incurable to hope for effective treatments. To date, both diseases still lack a comprehensive understanding of disease progression despite the rich pipeline of promising therapeutic candidates. However, as exciting it is to witness the growth in drug development and investments from biotech sector, there are insufficient numbers of patients to enroll across these trials. This is astounding considering that just 20 years ago there were few trials being conducted. Both diseases have prominent and vocal patient advocacy communities with a driving sense of urgency and a strong voice for change and innovation.

Advocacy communities have led the development of draft guidance documents submitted to the FDA, one for DMD in 2018[16] and one for ALS submitted in 2020.[17] Recommendations included a request to omit placebo arms from clinical trials or, alternatively, acceptance of virtual controls, accelerated approvals via biomarkers as surrogate outcomes, and pre-market access permits to medicines. The EMA in recognition of the increasing number of clinical trials has published guidances on ALS[18] and DMD[19] in 2015 which clearly communicates similar themes. Clearly, all stakeholders recognize that there is a tremendous sense of urgency for therapeutics; yet, in many cases, there is a perceived sense of concern that regulators are delaying progress. From the regulatory perspective, it is the duty of regulators to ensure that medicines are appropriately authorized for both safety and efficacy, which requires clinically robust and target relevant data.[20] Effective communications of all stakeholders and true urgency for collaboration is key.

### Learning and insights from clinical trials

Much can be learned about diseases and conduct of future trials by gaining access to clinical trial data, particularly from the negative outcomes of investigational agents tested.[21,22] Insights gained from analysis of clinical trial data across the spectrum of success can accelerate research progress that can, in turn, drive the design of innovative clinical trials. DMD and ALS clinical trials are paving the way for groundbreaking and collaborative strategies applicable to many other areas and to the benefit of patient communities and public health.

For example, the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Database is the largest publicly available repository of merged ALS clinical trials data.[23] The vision of the PRO-ACT project was to accelerate and enhance translational ALS research by designing and building a data set that would contain the merged data from as many completed ALS clinical trials as possible. PRO-ACT was launched as an open-access platform for researchers in December 2012 and represents one of the first examples showing the success of crowdsourcing to incentivize novel discoveries.[24] The PRO-ACT database enabled a community of thousands of users throughout the world.[23] The database consists of patient-level data from over 10,000 patients derived from a total of 23 phase II and phase III ALS clinical trials. This is a remarkable achievement, particularly for a rare disease. Since its launch, the PRO-ACT database has become the database that global new initiatives are spearheading with the goal of expanding and enriching new data to inform the many clinical trials underway. The PRO-ACT initiative has greatly enhanced the design of ongoing ALS clinical trials and new trials are being integrated to ensure that the database consists of contemporary trial data.[25]

### Multi-arm adaptive platform trials

Although robust evidence generation is necessary to facilitate access to safe and effective treatments, the heterogeneous, fast-progressing, and rare nature of ALS presents challenges that could be addressed with the use of efficient, innovative trial designs. A comprehensive and innovative platform multi-arm trial initiative has been launched for ALS borrowing from the successes in cancer drug development. This design allows multiple drug candidates to be tested in parallel using specialized statistical tools and shared placebo arm groups.[26] The approach holds promise for reduced burden in terms of trial costs, accelerating timelines for patient recruitment, and allows a ready cohort of subjects with well-characterized phenotypes.[27] As of 2021, there were 30 applicants from 10 countries that have submitted proposals to the HEALEY ALS Platform trial ALS trial design team.[28] A second ALS MAMS trial is underway in Europe.[29] The Motor Neuron Disease (MND) Systematic Multi-Arm Adaptive Randomized Trial (MND SMART) is being sponsored by the University of Edinburgh with funding from a number of charitable organizations and has recently been reviewed by regulators. Multi-arm platform trials are also being planned in DMD (unpublished) and other nervous system disorders. The FDA guidance for Platform Trials "Adaptive Design Clinical Trials for Drugs and Biologics" was issued in 2019.[30]

### Guidance and Digital Health Technologies

The regulatory landscape for advancement of digital health technologies (DHTs) in medicines development and use is rapidly

evolving, with an increased inclusion as part of the conduct of clinical trials. Necessary innovations in development, use, and deployment of DHTs were accelerated by the COVID-19 pandemic because of the need to reduce person-to-person contacts, and to support remote data gathering and study monitoring. Such approaches also reduced participant and staff burden.[31] Specific procedures to present and validate DHTs for regulatory feedback are emerging, including the EMA qualification of novel methodologies.[32,33] Notably, in 2019, the EMA qualified the use of 95% stride velocity as assessed using a wearable device as a secondary end point for clinical trials in DMD.[34]

In disease areas such as ALS, disease-specific guidance highlights how DHTs can be informative and potentially transformative. The FDA guidance of September 2019, focused on specific clinical drug development and trial design issues that are unique to ALS.[35] As part of the ongoing emphasis of the FDA on greater patient engagement at every phase of drug development, the guidance emphasizes that "Sponsors should understand how affected patients view treatment goals and risk tolerance," and sponsors were asked to also consider novel technologies (e.g., wearable biosensors), as appropriate. Integrating digital measures with clinical assessments of disease progression could enable adaptive platform trials thereby accelerating validation of their use.

### Public-Private Partnerships advancing science through cross-disciplinary collaboration, and neutral multistakeholder platforms

The Critical Path Institute (C-Path) was formed in 2005 in response to the FDA Critical Path Initiative, which identified public-private partnerships and consortia as fundamental to scientific advancement and innovation in medical product development.[36] The C-Path leads public-private partnerships designed to facilitate discussion and interaction among relevant stakeholders, including regulatory agencies. They act as a trusted, neutral third party for sharing of data, tools, and expertise required for the development of novel methodologies and drug development tools.[37]

The C-Path Duchenne Regulatory Science Consortium (D-RSC) has aggregated data and shared expertise from multiple sources and currently holds patient-level data from nearly 5,000 patients across various stages of DMD. These data have been applied to the development of a series of disease-progression models that reflect the variance among DMD populations and maps progression using stage-specific outcome measures. By applying these findings to the development of a clinical trial simulation tool, the D-RSC has been able to better understand the natural progression of DMD and identify outcome measures with applicability across the spectrum of the disease.[38] The ultimate goal for D-RSC is to develop a clinical trial simulation platform that facilitates regulatory endorsement under the umbrella of model-informed drug development.

### From orphan to common brain disease—Parkinson's disease

How can we translate innovations emerging in rare diseases to common diseases of high prevalence? The most rapidly growing brain disease of all is Parkinson's disease (PD). The number of people with PD has more than doubled from 1990 to 2015 and could double again by 2040.[39]

A rich and promising pipeline of therapeutic candidates currently in development for the treatment of PD advances the potential for effective disease modification.[40] The current portfolio of clinical trials is aimed at a diversity of therapeutic targets with increasing attention focused on biological pathways related to genetic variants.[41] A growing number of genetic forms of PD are now being pursued as therapeutic targets for disease modification.[41] Such advances have catalyzed investments from the biotech community and led to a rich expansion of research that includes early intervention stratified by genetic status in at-risk individuals.[42] Encouragingly, the PD pipeline has remained strong despite the global COVID-19 pandemic.[43] The outlook for effective PD therapeutics is tempered by an extraordinarily high failure rate of PD trials, particularly for those that target disease modification.[44] A variety of reasons have been proposed, including lack of translational validity of preclinical models, failure of agent to reach and engage target adequately, unknown mechanisms of action for many candidates, confounding of currently approved symptomatic therapy, and absence of objective measures of true disease progression.[45]

Lessons learned from clinical trial design and conduct for rare diseases could serve as a platform for regulatory strategies for addressing high incidence brain disorders. The rapidly evolving era of precision medicine for PD and other high prevalence neurodegenerative diseases provides a foundation on which to target specific genotypic and phenotypic forms of PD. In that regard, the strategies that apply to orphan drug designation can be applied to targeting genetic forms of PD.

### Multi-arm Platform Clinical Trial for PD

As demonstrated in rare disease and oncology, multi-arm, multi-stage (MAMS) trial platforms promise to overcome challenges in conducting trials in areas of unmet needs, such as PD. A MAMS trial platform is being planned for PD in the United Kingdom with current efforts aimed at achieving consensus on (i) drug selection, (ii) an appropriate patient population for study, (iii) methodology for identifying disease modification and whether this is necessary, as well as (iv) effective and relevant outcome measures.[46] To reach consensus on these issues in PD, a Delphi process is currently being developed to inform the design of a MAMS platform.[47] This method is an iterative approach whereby experts from different backgrounds, such as clinicians, funders, industry, academics, regulators, and patients, complete multiple rounds of iterative questionnaires based on previous responses to enable a process to arrive at a consensus.[46]

**Innovative Technologies to monitor disease progression.** Digital health technologies are being developed that can collect vast amounts of data around the clock and facilitate analyses to produce a more comprehensive picture of Parkinson's symptoms. Remote monitoring allows a precise characterization of disease-specific signatures through analyses of big and complex datasets of both in-clinic and at home measurements. As digital devices have begun to be integrated into Parkinson's observational and clinical trials, there is growing interest in

the regulatory acceptance of these tools for decision making for advancing new therapies to patients. Collaborations are needed to tackle the challenges that this rapidly advancing field faces, particularly because their applications to healthcare while offering innovative solutions will require appropriate validation and the support of Regulatory Agencies.[33,48] The Digital Drug Development Tools (3DT) group has been created under the auspices of C-Path's Critical Path for Parkinson's (CPP) consortium as a dedicated team that is sharing knowledge and data in the precompetitive space. A staged plan has been initiated which aims to advance a data-driven collaboration framework to collectively advance the field in a device-agnostic way. Such an approach would allow multiple device platforms to be included in contributing to regulatory endorsement as a drug development tool platform solution tied to defined concepts of interest and contexts of use. CPP is leveraging the ongoing, prospective study called WATCH-PD (Wearable Assessments in The Clinic and Home in PD, NCT03681015), a multicenter, prospective, longitudinal, digital assessment study of PD progression in subjects with early, untreated PD, as an exemplar pilot study to facilitate discussion and alignment with regulatory agencies on evidentiary considerations for DHT for drug development.[49]

**Linking the voice of the patient with model-informed drug development.** Quantitative system pharmacology (QSP) models represent a mechanistically driven drug and disease modeling that seeks to address a diverse set of problems in the discovery and development of therapies. The goal of QSP models is to inform the decision making in early phase drug development by characterizing biological systems and disease processes to provide a mechanistically driven quantitative assessment of drug pharmacology.[50] QSP models also take significant time and effort to create when compared with statistical or classical empirically driven models; mostly because of the length of time to identify, evaluate, and populate credible model priors. A recent initiative of the CPP consortium involves the construction of a platform that receives data from a community-centric crowdsourcing approach that includes patients (patient swarm) so that model priors can be more efficiently catalogued and evaluated by data curators and QSP modelers. Crowdsourcing efforts will be evaluated as the model is being constructed and the patient swarm will be engaged to comment on both the structure and its predictive potential to explain disease progression and evaluate historical and current development candidates in real-time. In addition, patient-generated disease trajectories will be used as a real-world data source to validate the model.

Upon completion, patient-level, real-world data will serve to verify that the model is able to generate synthetic data that more closely mimics the heterogeneity of the family of disease etiologies currently classified as PD. People living with PD will describe their disease trajectories in quantitative terms with the help of an experienced QSP modeling team, some of whom will construct a model based on priors collected from all available sources (public and private sector) using an artificial intelligence/machine learning driven text mining approach to identify source data from the literature.

### Opportunities for the future

The progress that has emerged across the three diseases highlighted in this review clearly provides candid examples that suggest that innovative trial design approaches with focus on sharing data and learnings hold promise to accelerate progress to drug approvals (**Figure 1**). However, most disease foundations and the research initiatives they fund are focused on a single disease. There is a need for cross disease platform initiatives that provide the infrastructure to share data, tools, and learnings. Such initiatives have the potential to avoid reinventing the wheel for each disease on how to effectively advance drug development tools, conduct bidirectional translational research, and minimize the gap defined as the valley of death.[51]

Organizations, such as C-Path, an autonomous organization with a global reach, are uniquely placed to facilitate and add meaningful insight to the necessary collaborative efforts among key stakeholders, including regulators with shared interests in any therapeutic or disease area. The FDA has recently recommended crowdsourcing and data sharing across multiple disease areas as catalysts to accelerating drug development.[52] The FDA funded C-Path rare disease cures accelerator data analytics platform (RDCA-DAP) provides a mechanism to collect, curate, and exploit a variety of rare disease data types, is a great example of a combination of data sharing, data standards, and focus on the patient voice with innovative clinical trials strategies that can accelerate drug development. The platform contains data from completed clinical trials, registries, and natural history studies, as well as preclinical experiments, and not only provides a mechanism to share data, but offers connectivity to sophisticated tools that include, for example, disease progression models and clinical trial simulation applications (**Figure 2**). Such tools and approaches can be applied to the benefit of patients and diseases outside of the rare disease field.

### Academic Institution success story: Center for Innovation in Brain Science University of Arizona

Regulatory expertise coupled with deep domain knowledge of disease phenotypes, clinical trial design, and statistical rigor can catapult clinical trial development within the university sphere that is rich in therapeutic potential and impoverished in a regulatory capacity. Collaborations that enable both therapeutic development and regulatory excellence are key to harvesting the substantial investment in university-based discovery and translational science. An example of such a collaboration is between the Center for Innovation in Brain Science (CIBS; https://cibs.uahs.arizona.edu/) at the University of Arizona and the Critical Path Institute (https://c-path.org/).

The CIBS is focused on age-associated neurodegenerative diseases and is a hybrid of a biotech ecosystem within a university environment. The goal of the CIBS research that spans discovery, data, translational, and clinical sciences is to develop effective disease-modifying therapies and cures for Alzheimer's, Parkinson's, multiple sclerosis, and ALS. Critical to achieving this goal is access to disease-focused regulatory expertise for the design and execution of innovative clinical trials that are efficient, targeted, and precision medicine enabling. An example of such a collaboration between the Critical Path Institute and CIBS is the phase II REGEN-BRAIN

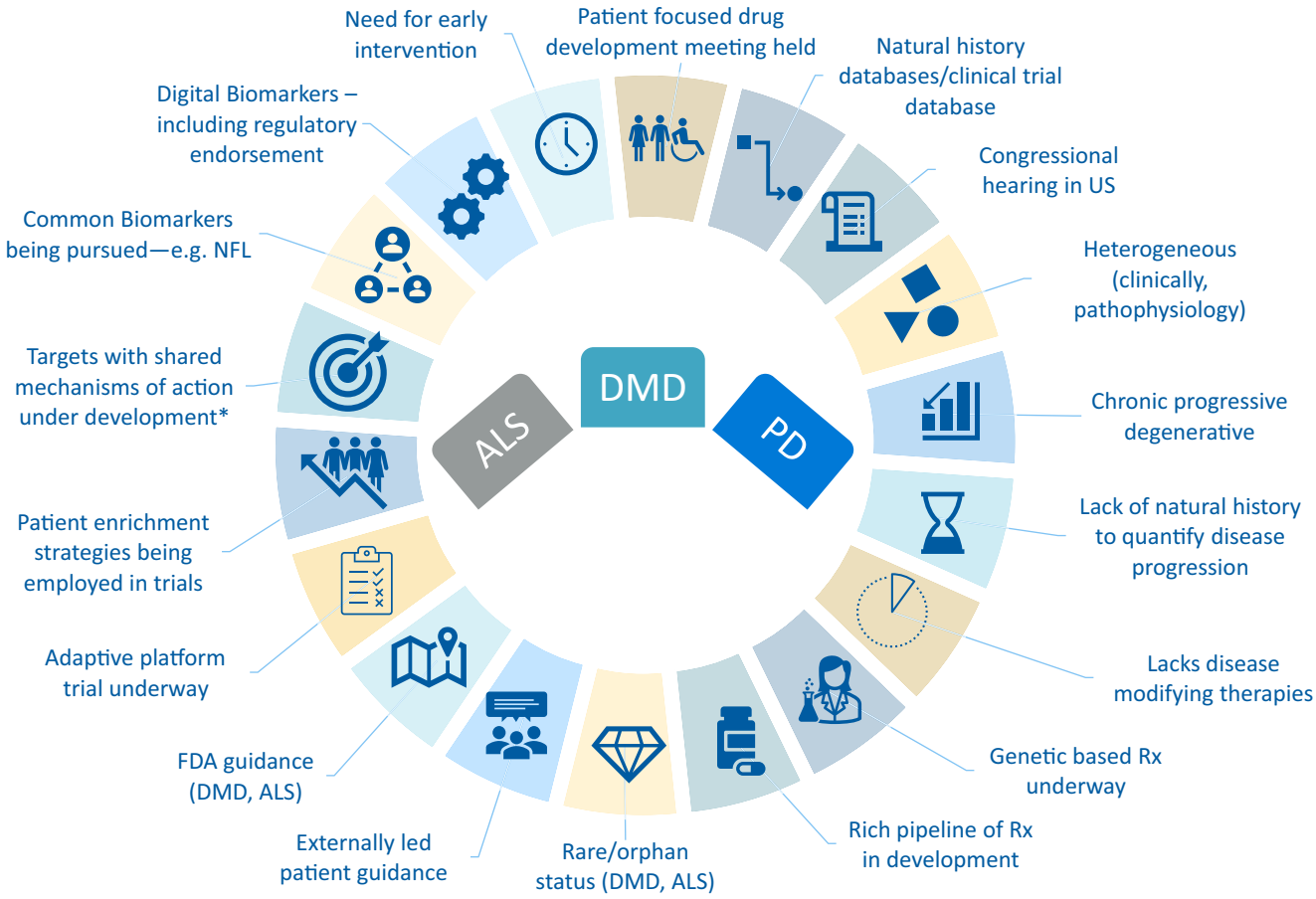


**Figure 1** Diagram highlighting examples of regulatory innovation, policy, and drug development in ALS, DMD, and PD. *Targets with shared mechanisms of action: oxidative stress, inflammation, mitochondrial stabilization, modulation of calcium homeostasis, restoration of energy homeostasis, stress response modulation, and growth factors. ALS, amyotrophic lateral sclerosis; DMD, Duchenne muscular dystrophy; EHR, electronic health record; PD, Parkinson's disease.

clinical trial to determine safety and efficacy of the first regenerative therapeutic for mild Alzheimer's disease to be conducted in persons carrying the Alzheimer's risk factor gene APOE4 (ClinicalTrials.gov Identifier: NCT04838301). The C-Path clinical trial simulation based on disease progression of APOE4 carriers was key to the novel clinical trial design and enrichment strategies.

Clinical trials of CIBS regenerative therapeutics for PD will be enabled by outcomes from the Parkinson's Progression Markers Initiative (PPMI) study, which found reduced striatal dopamine transporter binding in patients with early motor PD that was a predictor of rapid decline in Unified Parkinson Disease Rating Scale (UPDRS) parts II and III.[53] Using dopamine transporter as an enrichment biomarker in PD trials will enrich clinical trials of novel therapeutics in rapidly progressing persons with idiopathic PD. Further, reliable assessment of real-time motor function was enabled by the development of The "Critical Path for Parkinson's Consortium 3DT Initiative: Early regulatory engagement to optimize paths for efficient use of digital health technologies in PD clinical trials" (https://c-path.org/critical-path-for-parkinsons-3dt-initiative-early-regulatory-engagement-to-optimize-paths-for-efficient-use-of-digital-health-technologies-in-pd-clinical-trials/)[49] is a key digital technology initiative designed with the FDA regulatory input to ensure compliance will advance clinical trials of novel regenerative therapeutics currently being developed at CIBS for PD. The breadth of regulatory expertise that drives Critical Path Institute innovation in data sharing, clinical trial design, and innovative disease progression monitoring serves as a critical bridge across the broad regulatory landscape and the university-based discovery to therapeutic development domains. Determination of effective strategies that have advanced orphan drug development to other disease categories has the potential to accelerate therapeutic success for age-associated diseases for which there are no cures.

## Summary and recommendations for the future

The emerging advances and astonishing rate of drug approvals in rare diseases promise to continue and will be accelerated by applying principles of regulatory innovation, data sharing, and enhanced collaboration amongst stakeholders across the globe and spanning different disease states. The development and maintenance of a shared clinical research infrastructure to support efficient evidence generation as well as the widespread adoption of tools and mechanisms for the sharing of data across studies are key components of effective, collaborative drug development efforts. Integrating patient input into the design and conduct

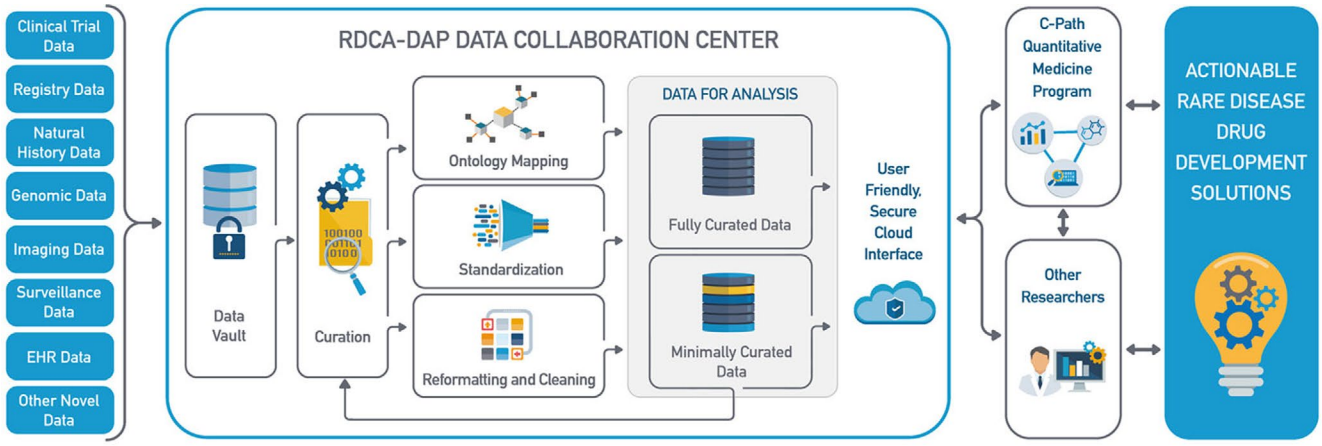


**Figure 2** The Critical Path Institute (C-Path)'s rare disease cures accelerator data analytics platform (RDCA-DAP) houses integrated patient-level data from diverse sources, including clinical trials, longitudinal observational studies, patient registries, and real-world data (e.g., electronic health records) across a multitude of rare diseases. Data are contributed from different organizations and companies around the world. Deidentified data is standardized, integrated, and analyzed to support regulatory endorsement of drug development tools.

of clinical trials is vital to advancing quality and innovation in drug development. Regulatory agencies are key collaborators in the ecosystem and can accelerate and incentivize progress in ways that are now being realized in rare diseases. Expansion of the pre-competitive space with prioritization on the needs of patients is needed to elicit changes that translate approvals for rare diseases into much needed treatments for chronic brain disorders as well.

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1. Feigin, V.L. *et al*. Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* **18**, 459–480 (2019).
2. Dowden, H. & Munro, J. Trends in clinical success rates and therapeutic focus. *Nat. Rev. Drug Discov.* **18**, 495–496 (2019).
3. Numbers, K. & Brodaty, H. The effects of the COVID-19 pandemic on people with dementia. *Nat. Rev. Neurol.* **17**, 69–70 (2021).
4. Fearon, C. & Fasano, A. Parkinson's disease and the COVID-19 pandemic. *J. Parkinsons Dis.* **11**, 431–444 (2021).
5. FDA New Drug Therapy Approvals 2020 Advancing Health Through Innovation <https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/new-drug-therapy-approvals-2020>.
6. REGULATION (EC) No 141/2000 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of December 16, 1999, on orphan medicinal products <https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-1/reg_2000_141_cons-2009-07/reg_2000_141_cons-2009-07_en.pdf>.
7. REGULATION (EC) No 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32006R1901&from=GA>.
8. European Commission: Commission Staff Working Document Evaluation. Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products <https://ec.europa.eu/health/sites/default/files/files/paediatrics/docs/orphan-regulation_eval_swd_2020-163_part-1.pdf> (2020).
9. Jahanshahi, M. *et al*. The use of external controls in FDA regulatory decision making. *Ther. Innov. Regul. Sci.* **55**, 1019–1035 (2021).
10. Mulberg, A.E. *et al*. Regulatory strategies for rare diseases under current global regulatory statutes: a discussion with stakeholders. *Orphanet J. Rare Dis.* **14**, 36 (2019).

11. FDA. FDA draft guidance on rare diseases: common issues in drug development guidance for industry <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-diseases-common-issues-drug-development-guidance-industry> (2019).
12. FDA. FDA draft guidance: IND submissions for individualized antisense oligonucleotide drug products: administrative and procedural recommendations guidance for sponsor-investigators <https://www.fda.gov/media/144872/download> (2021).
13. FDA. FDA draft guidance: Nonclinical Testing of Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases Guidance for Sponsor-Investigators <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/nonclinical-testing-individualized-antisense-oligonucleotide-drug-products-severely-debilitating-or> (2021).
14. Chiò, A. *et al*. Global epidemiology of amyotrophic lateral sclerosis: a systematic review of the published literature. *Neuroepidemiology* **41**, 118–130 (2013).
15. Crisafulli, S. *et al*. Global epidemiology of Duchenne muscular dystrophy: an updated systematic review and meta-analysis. *Orphanet J. Rare Dis.* **15**, 141 (2020).
16. Furlong, P. *et al*. How a patient advocacy group developed the first proposed draft guidance document for industry for submission to the U.S. Food and Drug Administration. *Orphanet J. Rare Dis.* **10**, 82 (2015).
17. Andrews, J.A., Bruijn, L.I. & Shefner, J.M. ALS drug development guidances and trial guidelines: consensus and opportunities for alignment. *Neurology* **93**, 66–71 (2019).
18. EMA Guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis (ALS) <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-amyotrophic-lateral-sclerosis_en.pdf>.
19. EMA Guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-duchenne-becker-muscular-dystrophy_en.pdf>.
20. Morgan, P. *et al*. Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival. *Drug Discov. Today* **17**, 419–424 (2012).
21. Petrov, D., Mansfield, C., Moussy, A. & Hermine, O. ALS clinical trials review: 20 years of failure. Are we any closer to registering a new treatment? *Front. Aging Neurosci.* **9, 68** (2017).
22. Haas, M. *et al*. The European Medicines Agency's strategies to meet the challenges of Alzheimer disease. *Nat. Rev. Drug Discov.* **14**, 221–222 (2015).
23. Atassi, N. *et al*. The PRO-ACT database: design, initial analyses, and predictive features. *Neurology* **83**, 1719–1725 (2014).
24. Küffner, R. *et al*. Crowdsourced analysis of clinical trial data to predict amyotrophic lateral sclerosis progression. *Nat. Biotechnol.* **33**, 51–57 (2015).
25. Goyal, N.A. *et al*. Addressing heterogeneity in amyotrophic lateral sclerosis CLINICAL TRIALS. *Muscle Nerve* **62**, 156–166 (2020).
26. The Adaptive Platform Trials Coalition Adaptive platform trials: definition, design, conduct and reporting considerations. *Nat. Rev. Drug Discov.* **18**, 797–807 (2019).
27. Saville, B.R. & Berry, S.M. Efficiencies of platform clinical trials: a vision of the future. *Clin. Trials* **13**, 358–366 (2016).
28. MASSACHUSSETTS GENERAL HOSPITAL HEALEY ALS Platform Trial - SEAN M. HEALEY & AMG CENTER FOR ALS <https://www.massgeneral.org/neurology/als/research/platform-trial>.
29. ClinicalTrials.gov Motor Neurone Disease - Systematic Multi-Arm Adaptive Randomised Trial (MND-SMART) - ClinicalTrials.gov Identifier: NCT04302870 <https://clinicaltrials.gov/ct2/show/NCT04302870>.
30. FDA. FDA guidance - adaptive design clinical trials for drugs and biologics guidance for industry <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry> (2019).
31. Ramanan, A.V. *et al*. Improving clinical paediatric research and learning from COVID-19: recommendations by the Conect4Children expert advice group. *Pediatr. Res.* https://doi.org/10.1038/s41390-021-01587-3. [e-pub ahead of print].
32. EMA. EMA guidance: qualification of novel methodologies for drug development: guidance to applicants. (2009).
33. Mantua, V., Arango, C., Balabanov, P. & Butlen-Ducuing, F. Digital health technologies in clinical trials for central nervous system drugs: an EU regulatory perspective. *Nat. Rev. Drug Discov.* **20**, 83–84 (2021).
34. Haberkamp, M. *et al*. European regulators' views on a wearable-derived performance measurement of ambulation for Duchenne muscular dystrophy regulatory trials. *Neuromuscul. Disord.* **29**, 514–516 (2019).
35. FDA. FDA guidance: amyotrophic lateral sclerosis: developing drugs for treatment guidance for industry <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/amyotrophic-lateral-sclerosis-developing-drugs-treatment-guidance-industry> (2019).
36. Woodcock, J. & Woosley, R. The FDA critical path initiative and its influence on new drug development. *Annu. Rev. Med* **59**, 1–12 (2008).
37. Woodcock, J., Brumfield, M., Gill, D. & Zerhouni, E. The driving role of consortia on the critical path to innovative therapies. *Nat. Rev. Drug Discov.* **13**, 781 (2014).
38. the Duchenne Muscular Dystrophy Regulatory Science Consortium (D-RSC) *et al*. Towards regulatory endorsement of drug development tools to promote the application of model-informed drug development in Duchenne muscular dystrophy. *J. Pharmacokinet. Pharmacodyn.* **46**, 441–455 (2019).
39. Dorsey, E.R. *et al*. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* **17**, 939–953 (2018).
40. Vijiaratnam, N., Simuni, T., Bandmann, O., Morris, H.R. & Foltynie, T. Progress towards therapies for disease modification in Parkinson's disease. *Lancet Neurol.* **20**, 559–572 (2021).
41. Sardi, S.P., Cedarbaum, J.M. & Brundin, P. Targeted therapies for Parkinson's disease: from genetics to the clinic: targeted therapies for PD. *Mov. Disord.* **33**, 684–696 (2018).
42. Schneider, S.A. & Alcalay, R.N. Precision medicine in Parkinson's disease: emerging treatments for genetic Parkinson's disease. *J. Neurol.* **267**, 860–869 (2020).
43. McFarthing, K., Rafaloff, G., Baptista, M.A.S., Wyse, R.K. & Stott, S.R.W. Parkinson's disease drug therapies in the clinical trial pipeline: 2021 update. *J. Parkinsons Dis.* **11**, 891–903 (2021).
44. Lang, A.E. & Espay, A.J. Disease modification in Parkinson's disease: current approaches, challenges, and future considerations: disease modification in PD. *Mov. Disord.* **33**, 660–677 (2018).
45. Devos, D., Hirsch, E. & Wyse, R. Seven solutions for neuroprotection in Parkinson's disease. *Mov. Disord.* **36**, 306–316 (2021).
46. Zeissler, M.-L., Li, V., Parmar, M.K.B. & Carroll, C.B. Is it possible to conduct a multi-arm multi-stage platform trial in Parkinson's disease: lessons learned from other neurodegenerative disorders and cancer. *J. Parkinsons Dis.* **10**, 413–428 (2020).
47. Zeissler, M. Informing the design of disease modifying trials for Parkinson's disease – A Delphi study. Movement Disorders Congress 2021; Abstract 452 <https://www.mdsabstracts.org/abstract/informing-the-design-of-disease-modifying-trials-for-parkinsons-disease-a-delphi-study/> (2021).
48. Sacks, L. & Kunkoski, E. Digital health technology to measure drug efficacy in clinical trials for Parkinson's disease: a regulatory perspective. *J. Parkinsons Dis.* **11**, S111–S115 (2021).
49. Stephenson, D. *et al*. Precompetitive consensus building to facilitate the use of digital health technologies to support Parkinson disease drug development through regulatory science. *Digit. Biomark.* **4**, 28–49 (2020).
50. Geerts, H. *et al*. Quantitative systems pharmacology for neuroscience drug discovery and development: current status,

opportunities, and challenges. *CPT Pharmacometrics Syst. Pharmacol.* **9**, 5–20 (2020).
51. Seyhan, A.A. Lost in translation: the valley of death across preclinical and clinical divide – identification of problems and overcoming obstacles. *Transl. Med. Commun.* **4**, 18 (2019).
52. Thompson, A. & Parekh, A. Value of data sharing to advance drug development: a regulatory perspective. *Ther. Innov. Regul. Sci.* **55**, 850–852 (2021).
53. Stephenson, D. *et al*. The qualification of an enrichment biomarker for clinical trials targeting early stages of Parkinson's disease. *J. Parkinsons Dis.* **9**(3), 553–563 (2019).