Institution: University College London		
Unit of Assessment: 4 Psychology, Psychiatry and Neuroscience		
Title of case study: Accelerating pioneering therapeutic trials of a treatment for Huntington's Disease.		
Period when the underpinning research was undertaken: 2008-2015		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Sarah Tabrizi	Director of Huntington's Disease Centre	1996-present
Rachel Scahill	Principal Research Fellow	1998-2007; 2008-present
Eileanoir Johnson	Research Fellow	2012-2020
Gail Owen	Clinical Trials Manager	2008-present
Period when the claimed impact occurred: 2015- present		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Huntington's Disease (HD) is a debilitating and fatal neurodegenerative illness affecting approximately 4-10 people per 100,000 population. There are currently no licensed disease-modifying treatments. The lack of robust markers for disease progression has hitherto hampered the development of therapies. A UCL-led international observational study of Huntington's disease has transformed understanding of disease progression and enabled the development of biomarkers and clinical tools that have accelerated major industry-led therapeutic trials in humans. These tools led directly to the world's first-in-human Phase 1b/2a trial of an antisense oligonucleotide (ASO) with promising results, leading Roche Pharmaceuticals to exercise a USD45m licence agreement to progress the drug. The tools are currently being implemented in a pivotal phase 3 trial, bringing a potential treatment for HD significantly closer.

2. Underpinning research

HD is a devastating inherited neurological condition, which leads to progressive loss of cognitive and motor function and the development of neuropsychiatric disturbance. It is caused by a mutation which codes for the production of the toxic mutant huntingtin protein that slowly damages neurons leading to brain dysfunction and cell death. Following the discovery of the gene in 1993, a predictive genetic test was developed allowing research teams to study gene carriers several years before the expected onset of clinical symptoms, known as the premanifest phase. Although some of the symptoms of the disease can be treated, there are currently no disease-modifying treatments licensed for HD. Novel therapeutic agents with the potential to halt or slow the underlying disease processes are in development, but there was an urgent need to identify sensitive, reproducible and robust markers of progression from the premanifest stage through to established disease in order to assess treatment efficacy.

From 2008 to 2014 Professor Tabrizi led the large multi-site observational *TRACK-HD* study **[R1]** funded by the CHDI Foundation, a not-for-profit organisation dedicated to finding treatments for HD. This study brought together a multi-disciplinary team of world experts in imaging, neuropsychiatry, cognitive and motor function and collected data from four internationally-renowned HD research centres: UCL, Leiden University Medical Centre, ICM in Paris and the University of British Columbia in Vancouver. *TRACK-HD* aimed to critically evaluate potential biomarkers for use in future clinical trials in HD by annual follow-up of a cohort of early-HD and premanifest gene carriers as well as healthy controls [**R2, R3, R4]**. Novel imaging, cognitive, motor, neuropsychiatric and biofluid measures, were standardised across sites and collected, quality controlled and monitored in a similar way to a clinical trial. A range of robust measures from multiple domains suitable for use in clinical trials and sensitive to disease effects across the spectrum of HD were identified **[R3]**. Notably, imaging measures identified brain changes in

premanifest gene carriers up to 15 years before the expected onset of symptoms, in the absence of a behavioural phenotype **[R1, R2, R3, R4, R5]**. This information is invaluable in identifying the optimum time window for intervention, since it raises the possibility of slowing or halting these degenerative processes whilst function is still intact. *TRACK-HD* has given rise to over 40 publications, including six articles in the *Lancet Neurology* and has resulted in the following measurable outcomes which have had a major impact on the field of treatment in neurodegeneration:

1. An unparalleled deep phenotypic database resource freely available for both the research community and pharmaceutical companies designing clinical trials for potential treatments in HD.
2. Development of validated biomarkers, standardised across multiple sites, for use in clinical trials:
    a. The first human assay for huntingtin, the toxic protein which causes HD pathology **[R5]**
    b. Measures of global and regional brain atrophy indicative of neuronal loss **[R2]**
    c. The composite Unified Huntington's Disease Rating Scale (cUHDRS), a functional measure of disease progression **[R6]** developed by Roche using TRACK-HD data in collaboration with TRACK-HD investigators.

As a direct result of her leadership of TRACK-HD, Tabrizi was appointed global lead investigator on a phase 1b/2a safety trial of the ASO drug IONIS-HTT$_{Rx}$ sponsored by Ionis Pharmaceuticals from 2015 to 2017. The trial demonstrated excellent safety and tolerability, as well as crucially showing treatment-related lowering of mutant huntingtin levels **[R7]**. Tabrizi is UK Chief Investigator, PI for the UCLH site, and a senior advisor on the strategic steering committee for the Roche Phase 3 efficacy trial in HD.

3. References to the research

[R1] Tabrizi, S. J., Langbehn, D. R., Leavitt, B. R. et al. (2009). Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. *Lancet Neurology*, *8(9)*, 791-801. doi: 10.1016/S1474-4422(09)70170-X

[R2] Tabrizi, S. J., Scahill, R. I., Durr, A. et al. (2011). Biological and clinical changes in premanifest and early stage Huntington's disease in the TRACK-HD study: the 12-month longitudinal analysis. *Lancet Neurology, 10(1)*, 31-42. doi: 10.1016/S1474-4422(10)70276-3

[R3] Tabrizi, S. J., Reilmann, R., Roos, R. A. C. et al. (2012). Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: analysis of 24 month observational data. *Lancet Neurology, 11(1)*, 42-53. doi: 10.1016/S1474-4422(11)70263-0

[R4] Tabrizi, S. J., Scahill, R. I., Owen, G. et al. (2013). Predictors of phenotypic progression and disease onset in premanifest and early stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. *Lancet Neurology*, *12(7)*, 637-49. doi: 10.1016/S1474-4422(13)70088-7

[R5] Weiss, A., Trager, U., Wild, E. J. et al. (2012). Mutant huntingtin fragmentation in immune cells tracks Huntington's disease progression. *The Journal of Clinical Investigation*, *22(10)*, 3731-6. doi: https://doi.org/10.1172/JCI64565

[R6] Schobel, S. A., Palermo, G., Auinger, P. et al. (2017). Motor, cognitive, and functional declines contribute to a single progressive factor in early HD. *Neurology*, *89(24)*, 2495-2502. doi: 10.1212/WNL.0000000000004743

[R7] Tabrizi, S. J., Leavitt B. R., Landwehrmeyer, G. B. et al. (2019). Targeting Huntingtin expression in patients with Huntington's Disease. *The New England Journal of Medicine*, *380(24)*, 2307-2316. doi: 10.1056/NEJMoa1900907. (*This publication of the trial's results was named by the journal as 'one of the most significant NEJM articles of 2019' and has received over 157 citations to date (Mar 2021): http://bit.ly/2PkOdQ3*)

4. Details of the impact

The robust, reproducible and sensitive markers of disease progression provided by TRACK-HD **[R1]** gave Ionis Pharmaceuticals the confidence they needed to move forward with a trial of a potentially disease-modifying treatment. These measures were well understood and their low variability clearly established, so they provided sufficient power to suggest relatively small sample size requirements. Importantly they set the standard for evaluating clinical trial results, enabling a greater understanding of the safety of this treatment and its efficacy in slowing disease progression.

Phase 1b/2a safety trial in HD (2015-2017), sponsored by Ionis Pharmaceuticals
In 2015 Ionis Pharmaceuticals instigated the world's first-in-human clinical trial of an ASO in HD **[S1],** aiming to lower levels of mutant huntingtin in patients with early HD. It was described by HD Buzz (the research newsletter for the UK Huntington's community) as "*the most exciting drug trial so far in Huntington's disease*" **[S2]**. The trial, led by Tabrizi, reported excellent safety and tolerability, with treatment-related lowering of mutant huntingtin levels. The extensive worldwide press coverage of the results demonstrates their status as a ray of hope for HD sufferers (of whom there are over 8,000 in the UK alone). The Chief Executive of the Huntington's Disease Association said "*This is a great day for the Huntington's community. Today's announcement of the results of the trial are of groundbreaking importance to families affected by Huntington's disease. Although there is still some way to go before the overall results are known, this is a big step forward*" **[S3]**. HD Buzz hailed it as "*one of the biggest breakthroughs in Huntington's disease since the discovery of the HD gene in 1993"* and the Guardian selected it as one of 2017's top ten positive news stories **[S2]**.

The ready-to-use and validated biomarkers in HD developed by TRACK-HD data were critical to the design of the Ionis trial, which was led globally by UCL:

- The first human assay for huntingtin was a primary outcome measure for the trial **[S1]**. ASO treatment aims to lower levels of mutant huntingtin (mHTT) with the hope of reducing the pathological effect of this toxic protein. Only with this validated assay were Ionis able to demonstrate target engagement and show a dose-dependent reduction in mHTT levels in response to treatment.
- The cUHDRS was an exploratory measure that assesses meaningful changes in disease progression. This tool suggested clinical improvement in those receiving treatment even in this small trial of just 46 patients.

Ionis praised the *"successful execution"* of Track-HD, which "*provides confidence in the feasibility of conducting quality clinical research in HD, which encourages drug development".* Moreover its "*extensive patient community outreach… demonstrated that HD patients were willing to participate in a multi-year study with a substantial time commitment. All drug companies that followed benefitted from Track-HD's impact on the HD community's commitment to research"* **[S4].** Tabrizi's appointment as Global Lead Investigator for the Ionis trial was an easy choice as she "*stood out as a key expert given her leadership of Track-HD"* **[S4].**

Phase 3 efficacy trial in HD (ongoing), sponsored by Roche
The promising results of the Ionis trial convinced pharmaceutical company Roche to exercise a USD45m licence for the drug. They proceeded rapidly to a Pivotal Phase 3 efficacy trial with 909 participants, which began in January 2019 and is due to continue until June 2022 **[S5]**. Roche's decision to licence Ionis' drug and proceed to efficacy trials was entirely dependent upon the results from the Ionis safety trial, which in turn were underpinned by the findings of *TRACK-HD.* As with the Ionis efficacy trials, Tabrizi has been integral to the design, implementation and interpretation of Roche's programme, acting as Global Academic Lead on the trial's Strategic Steering Committee, drafting the trial protocol, and leading the UCL/UCLH study site as PI.

The design of the large and global Phase 3 efficacy trial **[S5]** (named GENERATION-HD1) has been strongly influenced by tools derived from TRACK-HD data, specifically the implementation of:

1. The cUHDRS as the global primary endpoint, with the support of the EMA.
2. The novel huntingtin assay, to assess levels of mHTT as a secondary outcome measure
3. Measures of regional and whole brain atrophy, as secondary outcome measures

Senior figures in Roche's clinical team state "*TRACK-HD has been a critical dataset for the design of GENERATION-HD1. […] For the development of potential therapies that target underlying disease pathology, it is critical to relate changes in clinical outcome assessments with candidate biomarkers. At the time, TRACK-HD was unrivalled in its ability to provide such timely and critical information that has advanced our understanding, and continues to serve as a critical reference sample against which we can evaluate clinical trial findings. The conduct of TRACK-HD is more similar to a clinical trial setting than other natural history studies, providing rates of change in both clinical outcome assessments and biomarkers that serve as a stronger reference against which to estimate potential placebo decline for use in study design and sample size calculations. The TRACK-HD dataset was the starting point for the creation of the cUHDRS, a scoring algorithm that combines four widely used scales into a single summary score. […] The cUHDRS is the global primary endpoint in GENERATION-HD1; therefore, TRACK-HD has provided a pivotal role in the development of the key determinant of success in a pivotal clinical trial*" **[S6].**

Alongside the pivotal Phase 3 trial, Roche are running a complementary Natural History study to chart disease progression in a matched 'control' group of participants **[S7]**. This study also uses the cUHDRS, mHTT assay and measures of brain atrophy developed in TRACK-HD.

Hope for the HD community

The significance of successful progress to the first long-term efficacy trial of a disease modifying therapy in HD to the patients, families and carers faced with realities of this devastating disease cannot be overestimated. In the weeks following the publication of results from the Ionis safety trials in December 2017, Tabrizi and her team at the HD Centre were inundated with thousands of emails from those affected by HD. A common theme throughout these messages and the numerous articles written on the disease since is one of hope: **[S8, S9]**

- *"I just want to express how much your study has given me and my family so much hope"*
- *"How exciting to read something that gives some hope!"*
- *"There has been no hope in the many years my father battled the disease until your research"*
- *"When the news broke yesterday it took my breath away, so much hope looking to the future"*
- *"I read the article on the trial that was just completed. It gives me great hope that one day this awful disease will be gone"* **[S10].**

5. Sources to corroborate the impact

[S1] Details of 2015 Ionis Trial from Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/results/NCT02519036?view=results

[S2] Collated sample media coverage of trial results.

[S3] Huntingdon's Disease Association article on trial results. https://www.hda.org.uk/news/major-breakthrough-in-huntingtons-disease-drug-trial

[S4] Supporting statement from Executive Director of Clinical Development, Ionis.

[S5] Details of Jan 2019 Phase 3 Roche trail from Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT03761849

[S6] Statement of support from senior representatives of Roche.

[S7] Details of Dec 2018 Roche Natural History Study from Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT03664804?term=Roche&cond=Huntington+Disease

[S8] 'At last, hope for families living in the shadow of Huntingdon's Disease'. *The Guardian*. March 2019. https://www.theguardian.com/science/2019/mar/03/huntingtons-disease-new-drug--families

[S9] 'Daring to Hope'. *Science Magazine*. August 2018. https://www.sciencemagazinedigital.org/sciencemagazine/24_august_2018/MobilePagedArticle.action?articleId=1418735#articleId1418735

[S10] Redacted emails available on request.