Cure Parkinson's Impact Report: March 2024

Cure Parkinson's (CP) publishes an annual report to evaluate the progress and impact of its research funding, and to reflect on the influence of facilitative work through the international Linked Clinical Trials (iLCT) programme. Understanding the strengths and weaknesses of our current funding will identify areas for improvement to ensure that CP funds and facilitates work in line with its mission: to find a cure for Parkinson's, urgently.

Impact reporting is encouraged by the Association of Medical Research Charities (AMRC) for this reason. The AMRC additionally requires member charities to hold a five-yearly review to evaluate their research funding strategy. In 2019 CP committed to continue funding clinical and pre-clinical research into potentially disease-modifying therapeutics that are at most five years away from clinical trial in Parkinson's. Specifically, this should focus on *funding* investigation into therapeutics via the iLCT programme and move towards *facilitation* in fields already receiving significant industry investment, such as cell therapies.

CP's funded research can be categorised according to its stage of research and focus, as defined in *Table 1*.

Stage	**Pre-Clinical**		Lab-based research evaluating potential therapies in models of Parkinson's
	Epidemiology*		Research assessing risk factors, distribution, and determinants of Parkinson's in collective populations
	Clinical	Phase 1b:	Clinical assessment of intervention safety in people with Parkinson's
		Phase 2:	Clinical assessment of intervention tolerability and efficacy in people with Parkinson 's
		Phase 3:	Clinical assessment of intervention efficacy in a large group of people with Parkinson's
	Infrastructure*		Projects supporting research logistics and efficiency, often facilitating collaboration
	Stratification*		Projects identifying subtypes of Parkinson's to create cohorts for clinical studies
	Other		Research to support clinical development that does not fall into the previous categories
Focus	**Prevent***		Interventions aiming to prevent the onset of Parkinson's
	Slow/Stop		Interventions aiming to slow or stop Parkinson's progression
	Reverse		Interventions aiming to regenerate dopaminergic neurons and disease regression.
	Other		Projects including infrastructure, genetic stratification, and biomarkers

Table 1 *The stages and focuses of CP funded research. *Please note that definitions marked with an asterisk have been analysed as 'other' projects for the purposes of this report.*

This report aligns with CP's 2024 research strategy review and provides an additional opportunity to evaluate how research funding impact has evolved over the last five years and how it might continue to evolve going forward.

Data up to 31 March 2024 has been evaluated in this report. To define impact the report will examine the scientific focus of funding and how this has changed over time, the progress of therapeutics through pre-clinical and clinical development, metrics of academic impact and the number of people with Parkinson's that have been involved with clinical research as a result of CP funding.

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Research Funding Updates: January 2023 – March 2024

CP currently funds 25 active projects, a commitment of almost £10.4 million. In the 15 months since the previous report, 11 projects have been *approved* for funding worth approximately £2.7 million. Five of these projects are now in progress and have been included in this analysis. These are pre-clinical investigations that will provide data on nine therapeutics and their disease-modifying potential in Parkinson's. *N.B The ASPro-PD trial is not included in these five however has been allocated to the 2023-2024 financial year and is included as such in analyses below.*

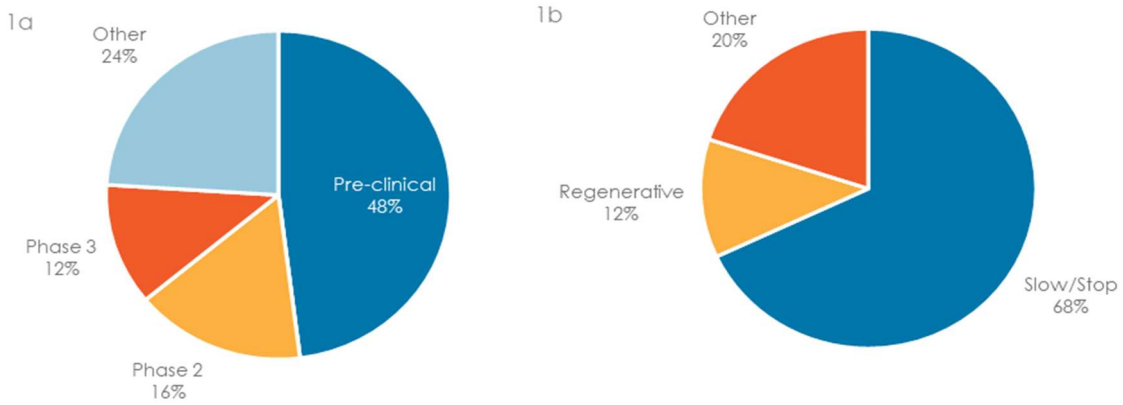


Figure 1a. *Stage of research receiving active funding.* ***1b.*** *Focus of research projects receiving active CP Funding.*

A majority of actively funded projects focus on slowing or stopping the progression of Parkinson's (68%, 17/25), reflecting an ongoing adherence to the 2019 research strategy review's recommendation that CP orient funding away from heavily industry funded areas such as cell and gene therapies which would look to reverse progression (*Figure 1*). Almost half of the funded projects are pre-clinical investigations of therapeutics (48%, 12/25). This increase since 2022 (reporting 32% of projects at the pre-clinical stage) occurs as a result of CP's commitment to funding final stages of research before clinical translation. A second funding programme, the iLCT Pipeline Research Acceleration Programme, was initiated in 2023 resulting in two new pre-clinical projects and a third contracted to begin in 2024. A summary of the iLCT Pipeline Research Acceleration Funding Programme can be found in Appendix 1.

These projects will ensure a rich pipeline of therapeutics with Parkinson's specific data to inform future clinical trials. However, this also highlights the need for active planning to facilitate further testing of successful therapeutics, potentially in clinical trial.

Five CP funded projects have additionally completed since December 2022. A summary of these projects and their initial impact can be found in Appendix 2.

Research Funding Overview: 2005 – March 2024

Since 2005, CP have funded or are currently funding 77 research projects. £17 million has been committed accumulatively and this will rise over the next year to more than £19.4 million with more than £2 million already committed (*Figure 2*).

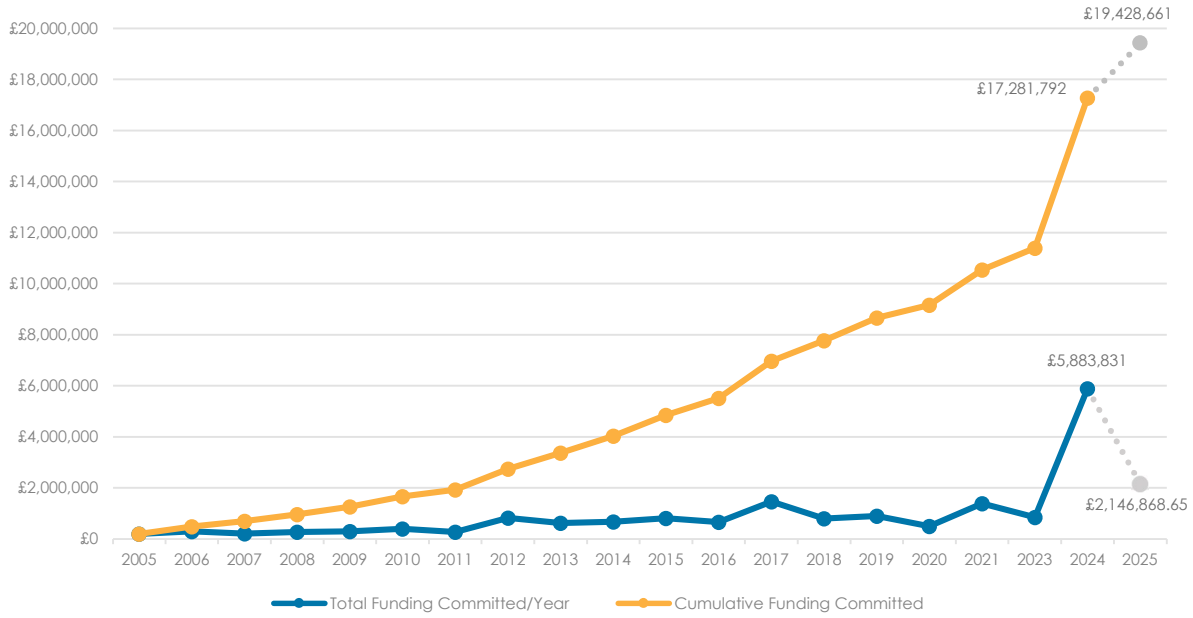


Figure 2 *Funding committed each year to CP projects (blue) compared to funding committed cumulatively since 2005 (orange). Figures in grey show funding currently committed to 2024-2025 or in the final contracting stages.*

Stage and Focus of Research Projects

Pre-clinical projects account for more than 50% of both active and historic grants (54.6%, 42/77) (*Table 2*). Aligning data with CP's five-year strategy reviews it is possible to see that the stage of funding has diversified in the last ten years compared to the ten before (*Figure 3)*. At the project level this reflects a move away from early pre-clinical and supportive projects towards pre-clinical work driving therapeutic development and clinical testing in people with Parkinson's.

	Active	Complete	Totals	% of all projects
Pre-clinical	12	30	42	54.55%
Phase 1	0	1	1	1.30%
Phase 2	4	6	10	12.99%
Phase 3	3	0	3	3.90%
Other	6	15	21	27.27%
Slow/Stop	17	25	42	54.55%
Regenerative	3	10	13	16.88%
Slow/Stop/Regenerative	0	3	3	3.90%
Other	5	14	19	24.68%

Table 2 *Number of projects funded by CP within each stage and focus of funding. Active and complete projects shown separately and as a percentage of the total projects funded.*

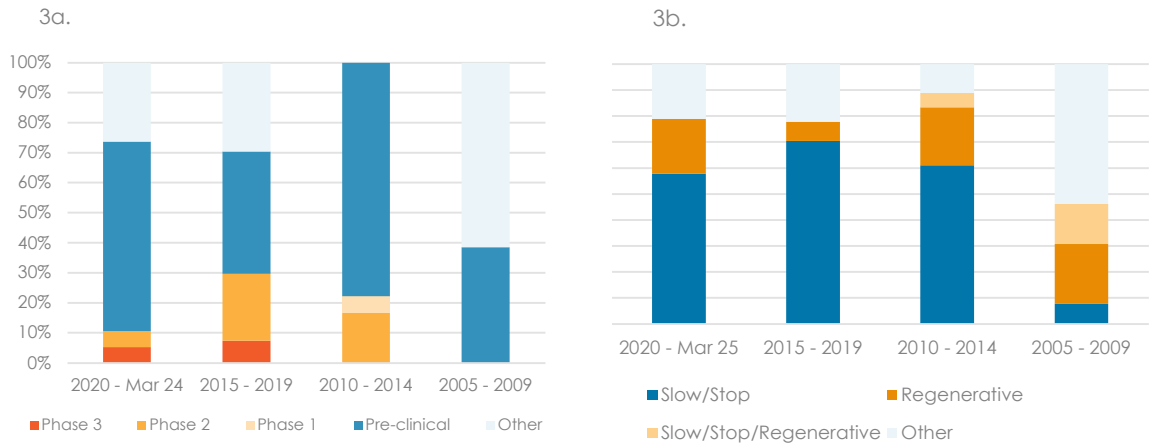


***Figure 3a**. The stage of projects funded within each five year period (2005 - March 2024). **3b**. The focus of research over each five-year period (2005 - March 2024) all as a percentage of the total projects within this time.*

Whilst the total number of clinical projects being supported by CP has remained relatively constant, total funding committed to clinical projects has increased as later stage trials are increasingly supported in their entirety. More than £5.7 million has been committed to clinical projects between 2020 and March 2024 with an additional £1.3 million already contracted up to March 2025, compared to £2.3 million committed between 2015 and 2019.

In response to its 2019 strategy review, CP has moved away from funding regenerative projects looking to reverse disease progression. A recent increase in projects in this area accounts for academic projects of innovative research that are looking to improve this space, for example novel delivery methods superior to the currently invasive administration of therapies. Additionally, the 'other' projects funded to support otherwise solely intervention-based research has reduced over time and the nature of those that remain now look to install infrastructure and research-accelerating mechanisms within the disease-modifying space. This is a move away from campaign support towards trial cohort stratification and development of technology to ensure ongoing and future clinical trials are given the greatest possible chance of success (*Figure 4)*.

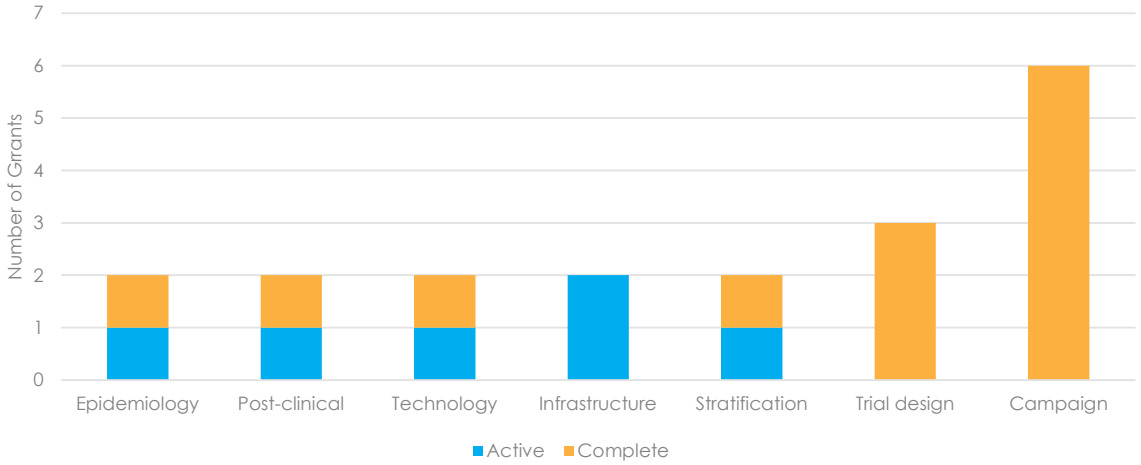


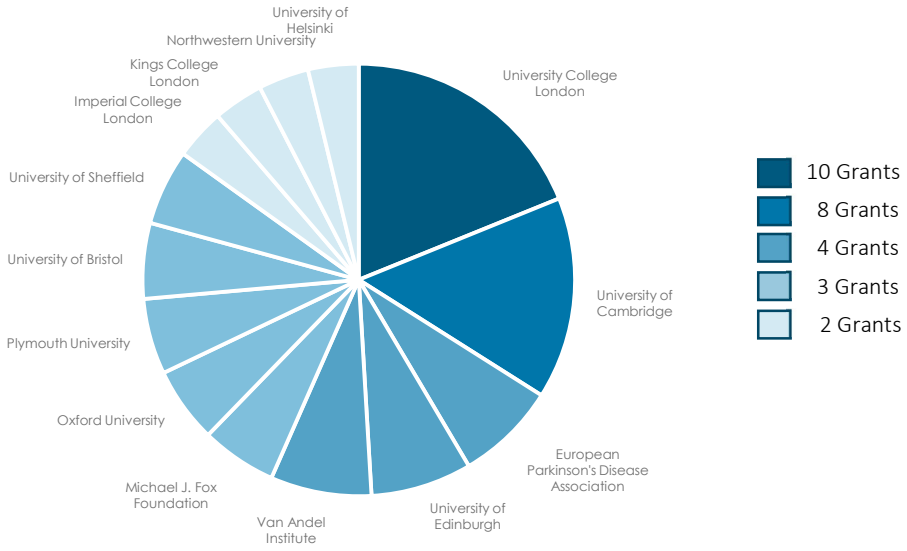
***Figure 4**. Focus of 'other' project grants, active (blue) and complete (orange), 2005 – 2024.*

Geography of Grants Awarded

CP have awarded funding for research in 38 institutions across 11 countries to 56 individual Principal Investigators (PIs) (*Figure* 6). Last year it was reported that the geographic reach of our grant funding programmes should actively be improved as more than half of all grants have been awarded to UK institutions. Whilst we were pleased to award grants in two new countries this year (Portugal, India), this should remain a priority with 65% (44/77) of grants overall awarded in the UK.

In the last year, to engage and encourage early career researchers within the field we have additionally introduced an 'internship' scheme with the CP Research Committee. This gives early post-doctoral or PhD researchers the opportunity to observe and take part in an active grant evaluation board to inform their future research both as an applicant and a potential reviewer. A web story was published at the end of 2024 which featured an interview with our first round of interns.

6a.



6b.

Aeon/ C.A.I.R institute	Loma Linda
Cardiff University	Lund University
Cedars-Sinai Medical Centre	Massachusetts General Hospital
EFNA	Neuronova
CHU de Toulouse	Queen Mary University of London
Indian Institute of Science Education and Research	Toronto Western Research Institute
Innervate Therapeutics	University College Cork
John Hopkins Institute	University of Queensland
John Radcliffe Hospital	Universite de Lille
Lancaster University	University Health Network, Toronto
Leeds institute of Molecular Medicine	University of Coimbra
University of New South Wales	
Weill Medical Centre of Cornell University	

6c.

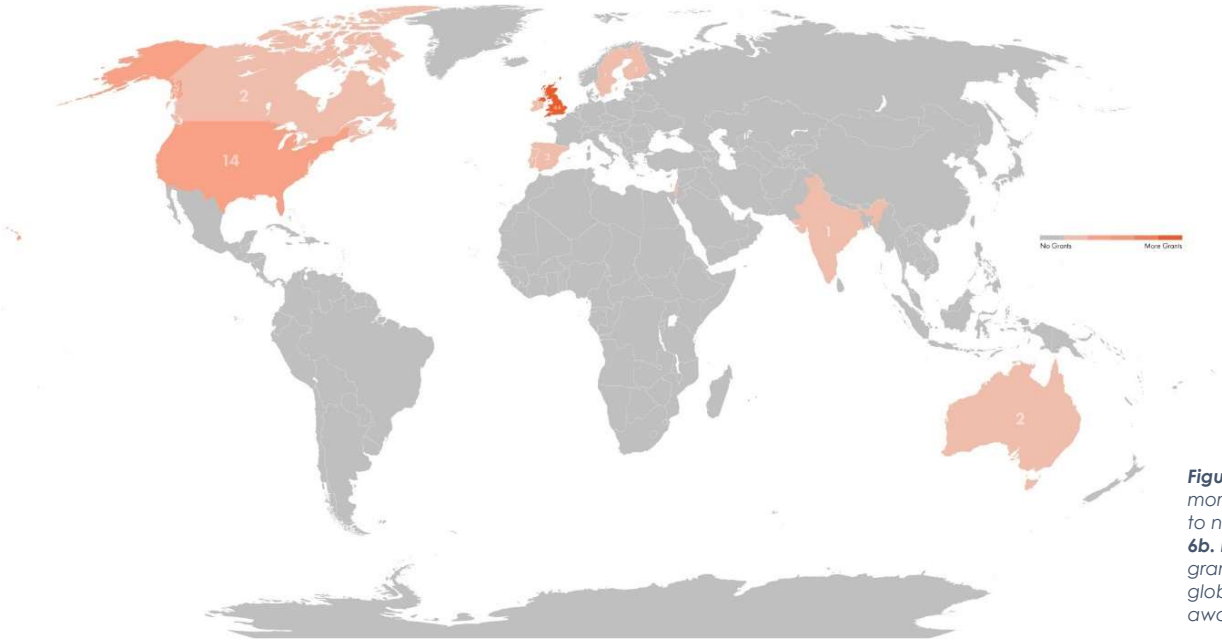
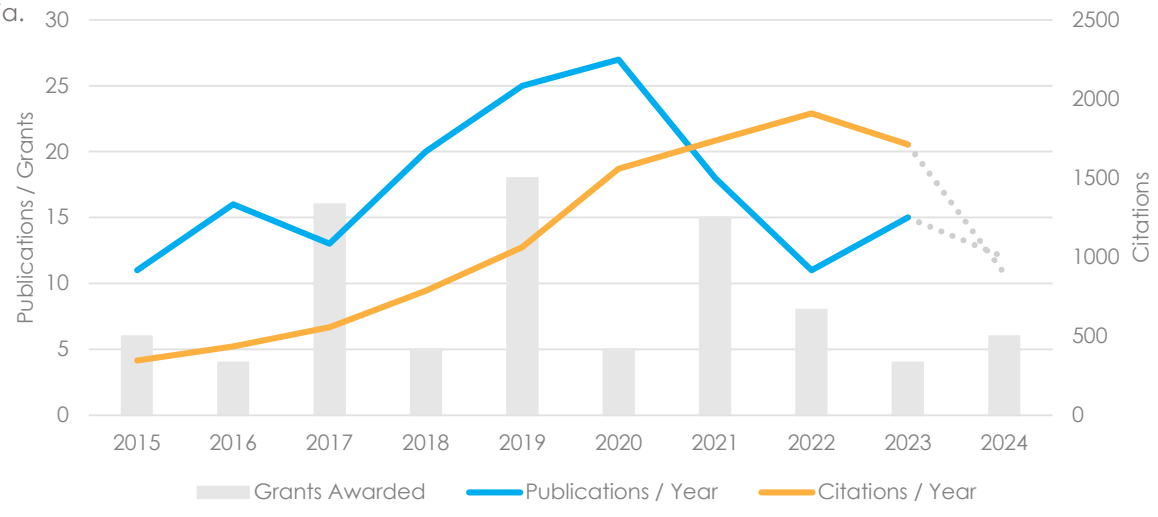


Figure 5a. *Institutions receiving more than one grant according to number of grants awarded.* ***6b.*** *Institutions awarded one grant.* ***6c.*** *Location of institutions globally, and number of grants awarded to each country.*

Academic Impact of Research Funding

Publication of funded research in peer-reviewed journals and the number of times these papers are cited in future publications can be used as an indication of research integrity and impact within the academic field. Dimensions, a dynamic platform that provides data for analysis and insight into research outcomes, funding and policy, estimates that approximately 209 papers have been published overall by CP funded PIs that cite CP funding. Whilst we do not expect these numbers to be exact due to variation in citations of funding, it is nevertheless encouraging to see numbers of publications begin to increase in 2023 after a dip seen in 2022, likely as a result of the pandemic (*Figure 7a*). Additionally, as in 2022, papers, although modest in number, remain broadly in line with the number of grants awarded over time and this is accompanied by increasing citations of these publications, with more than 11,600 total citations reported. Direct referencing of CP funded research evidences the growing impact that this research and subsequent publications are having in the broader academic field.

7a.



7b.

	Publications	Citations	Mean Citations
Bronze	20	1965	98.25
Hybrid	51	3614	70.86
Green	43	2454	57.07
Closed	37	1671	45.16
Gold	58	1893	32.64

*Figure **6a.** Number of publications, citations and grants per year. **7b.** Publications at each level of access: Gold (all articles immediately available, licensed for sharing), Bronze (free to read on publisher, no identifiable license), Green (work also posted to open repository, free to download), Hybrid (Paid access or subscription to articles only), Closed (Publisher provides pen access for articles if authors pay a publication fee). Data as of 25/06/2024.*

In 2022, we reported the importance of open access publishing to guarantee academic and wider media impact. Whilst a majority of papers are being published with some level of open access (172/209), closed access papers are, on average, being cited more than those with gold standard open access suggesting the academic weight that these papers hold (*Figure 7b)*. Continued emphasis on publishing open access will hopefully help to ensure that the results from CP funded research can be broadly and accessibly disseminated.

Approximately 375 institutions have been involved in publications citing Cure Parkinson's funding in at least 32 countries. 45 institutions have been involved with more than 5 Cure Parkinson's-associated papers, with University College London (UCL) publishing at least 60 papers citing funding. The institutions and PIs frequently publishing citing CP funding is broadly in line with the number of grants received, with the National Hospital of Neurology and Neurosurgery prominent due to its links with UCL.

CP were pleased to see results from two Phase 2 trials published in the last 15 months:

The UP Study: A Phase 2 study of UDCA in Parkinson's

Payne, T. et al (2023). A Double-Blind, Randomised, Placebo-Controlled Trial of Ursodeoxycholic Acid (UDCA) in Parkinson's Disease. Mov Disord, 38(8). doi:10.1002/mds.29450.

LixiPark: A Phase 2 study of lixisenatide in early Parkinson's

Meissner, W. et al (2024). Trial of Lixisenatide in Early Parkinson's Disease. New England Journal of Medicine, 390(13), doi:10.1056/NEJMoa2312323

Progress of Therapeutics

CP's funding remit specifies that grant funding is prioritised towards evaluation of potentially disease-modifying interventions that are at most five years from clinical trial in people with Parkinson's. Understanding how project results have influenced the progress of therapeutics through the pre-clinical and clinical pipeline is key to understanding the impact of our funding.

Since 2005:

- Cure Parkinson's have funded investigation into **41** individual therapeutics in **50** projects.
- Of these, **27** have been evaluated by the iLCT Committee and **12** prioritised for clinical trial.
- **76%** (31/41) of these therapeutics remain of interest for disease-modification in Parkinson's.

Of those that aren't of interest: 5 have been actively discontinued in the context of Parkinson's, 2 have been 'overtaken' by more promising drugs within the same class, and 3 remain of potential interest but are not actively being moved forwards at this time.

- Of those of interest: **23%** (7/31) are in active clinical trial, **26%** (8/31) have recently completed clinical trials and **42%** (14/31) are in active pre-clinical projects funded by CP
- **23%** (7/31) have moved onto subsequent stages of clinical research after completion of CP funding

Cure Parkinson's have directly funded **13** clinical trials involving more than **1320** people with Parkinson's.

The impact of iLCT

More than half of CP-funded therapeutics have been evaluated by the iLCT committee, leading to two Phase 3 clinical trials and multiple drugs tested at Phase 2. iLCT prioritisation has facilitated significant funding from external sources ensuring that promising therapeutics are actively guided along the clinical pipeline. 31% of all the drugs being actively tested in disease-modifying trials for Parkinson's have been evaluated by the iLCT Committee (McFarthing et al 2024, Appendix 3).

71% of all CP funding (£12.3 / £17.4 million) has been awarded to iLCT-related projects. More than £100 million of external funding has been facilitated via the iLCT programme to support clinical trials. The impact of the programme continues to grow as therapeutics reach later stages of clinical trial, providing access to potentially disease-modifying drugs to increasing numbers of people with Parkinson's. A full report of the impact of the iLCT Committee over the last 12 years has recently been published in the Journal of Parkinson's Disease:

Wyse, R. et al. (2024) Twelve Years of Drug Prioritization to Help Accelerate Disease Modification Trials in Parkinson's Disease: The International Linked Clinical Trials initiative. J. Parkinson's Dis. https://doi.org/10.3233/jpd-230363

It is estimated in this report that 41 complete and ongoing trials have been associated with the iLCT initiative. It is difficult to estimate the extent of the programme and Committee's influence more broadly, however looking at *all* clinical trials of iLCT-evaluated drugs starting after evaluation it is possible to expand this to:

- **14** therapeutics are currently being tested in **19** active clinical trials, involving **2351** people with Parkinson's.
- **18** have previously been tested in **24** complete trials, involving **2822** people with Parkinson's.
- Research has been conducted in at least **15** countries.

Conclusion

In December 2022, we posed three questions which we hoped to address to improve impact over the following 15 months.

1. How to expand the reach of our research funding opportunities
2. How to get more iLCT clinical trials underway
3. How to disseminate the findings of our funded projects more broadly

In 2023, we received our third highest number of applications over one year, almost double the number received in 2022. Through introduction of a commissioned funding programme, CP proactively sought applications for projects that directly align with our funding strategy, resulting in six full applications and additional expressions of interest. There was an internal focus on making connections through research events, meetings and conferences to directly disseminate information regarding CP's funding programmes. Over the next 12 months, a grant management system will be implemented to ensure capacity to manage increasing applications and grants. In addition, a formalised expression of interest process may be

explored to ensure that full applications, requiring extensive time from multiple stakeholders to complete, are of interest and within remit.

Following the annual iLCT Committee meeting, the CP team have been actively stewarding applications for further study of therapeutics, from evaluation to funding. These may be through the new iLCT Pipeline Research Acceleration Programme or through an open application. As a result of this, three out of five new projects in the last year are associated with iLCT therapeutics, in addition to the Phase 3 trial of ambroxol. With two clinical trials of iLCT-prioritised drugs due to begin in Summer 2024, the results of this active approach continue to unfold. As this process continues to evolve, it may be of interest to look at mechanisms for accelerating this process – from evaluation to trial.

CP continue to follow up and promote publications of funded research, with numbers of publications increasing over the last 12-15 months. Open access publication has not been requested at this stage due in part to financial implications, however this will continue to be looked into and encouraged wherever possible.

Looking forwards:

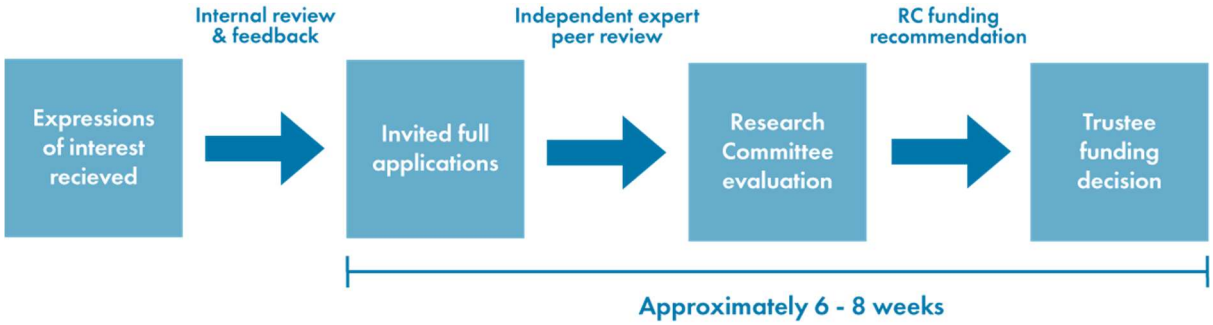
CP funded and supported research continues to result in impact in terms of academic publications, progress of therapeutics and availability of potentially disease-modifying treatments to people with Parkinson's. Looking forwards, this report has highlighted key areas for improvement:

- Ensuring that we receive and facilitate applications from a broad range of researchers, in part by -
- Collecting and analysing data to improve the equality, diversity and inclusion within our applicants and grant holders,
- Ensuring that therapeutics of interest from preclinical studies are rapidly translated into the clinic,
- Improving access to research for people with Parkinson's.

Appendix 1. The iLCT Pipeline Research Acceleration Programme

The international Linked Clinical Trials (iLCT) programme aims to speed up the search for disease-modifying therapies through prioritisation of therapies for clinical trial in Parkinson's. It is centered around an annual two-day meeting at which a committee of Parkinson's experts evaluate, rank and prioritise 15-20 drugs and compounds, often repurposed, based on their suitability for disease-modifying clinical trial for Parkinson's. CP's research team produce dossiers of each therapeutic for evaluation to ensure an unbiased approach. No funding is attached to this initiative and, currently, therapies are not evaluated in the context of a particular trial or study. However, prioritisation by the Committee results in a mandate that the therapy is tested in clinical trial. As a result of this, many applications that Cure Parkinson's receives are connected to iLCT-evaluated therapies.

The iLCT Pipeline Research Acceleration funding call was set up with the objective of accelerating additional research required for therapeutic candidates evaluated by the iLCT committee and considered of interest, but not ready to move forward into clinical trial. The type of research covered by this programme may include preclinical, epidemiological, dose-finding, or target engagement research. A previous example of a project funded within this programme can be seen here.



An open call is made annually for applications in response to a project outline developed by CP, investigating agents of interest to the iLCT committee. Expressions of interest received are reviewed internally to ensure they meet the project criteria before applicants are invited to work with Cure Parkinson's to submit a full application. Full applications will then be sent for external expert peer review, including at least one reviewer from the iLCT committee. Considering the peer reviews of each application, the research committee evaluate the applications and make a funding recommendation to Cure Parkinson's trustees.

Appendix 2. Impact of individual grants ending between January 2023 and March 2024

AW02: PD Sensors
Dr Alan Whone, Bristol University

Dr Whone received funding to support investigation of home-based sensors able to monitor people with Parkinson's symptoms while they move and live freely. The Bristol 'Sphere House' has been equipped with sensors to collect data showing symptom changes over time and how these affect activities of daily living. Accurate, continuous measurement can show nuanced changes in Parkinson's progression and this project will contribute to the ongoing unmet need for sensitive assessment measures to evaluate potential therapeutics. This grant resulted in publications exploring the datasets gathered and the experiences of participants living amongst these cameras and sensors to understand their acceptability.

Morgan, C. et al (2023) A multimodal dataset of real world mobility activities in Parkinson's disease. Scientific Data, 10.

Morgan, C. et al (2022) Acceptability of an In-Home Multimodal Sensor Platform for Parkinson

Disease: Nonrandomized Qualitative Study. JMIR Hum Factors, 9(3). https://doi.org/10.2196/36370

EL01: The LEARN TransEUro Study
Dr Emma Lane, Cardiff University

Dr Lane, alongside collaborator Dr Cheney Drew, collated and evaluated the experiences of participants and care partners involved in the TransEUro cell transplantation trial through a series of qualitative interviews. This information was developed to create a suite of resources to inform public communication for previously unsupported areas within clinical trial participation. The impact of this project will have broad implications as the pipeline of cell and gene therapy trials continues to grow. The trial team continue to work alongside research teams and companies within this space to share their learnings, embed best practices in future clinical trial design and ensure that future participants are safeguarded within these often invasive trial experiences.

Participation Resources: https://www.eurogct.org/learn

Lane, E. et al. (2022) Chapter Eight - More than a participant in trials of cell and gene therapy: Hearing the voices of people living with neurodegenerative diseases. International Review of Neurobiology, 166. https://doi.org/10.1016/bs.irn.2022.09.007

AC01: Stratification for GBA therapeutics
Prof Antony Cooper, University of New South Wales

Prof Cooper was awarded funding to assess the genetic signatures of people with Parkinson's to understand if individuals may be stratified to the most relevant GBA-related drugs for their Parkinson's. Given the increasing number of 'GBA' focused drugs in the Parkinson's Clinical Pipeline and CP's ongoing commitment to support clinical testing of ambroxol, where half the participants will carry a GBA mutation, the potential to stratify patients most likely to benefit is particularly of interest.

MS01: C-CDNF
Prof Mart Saarma, University of Helsinki

Prof Saarma was funded to undertake a preclinical investigation to optimise and characterise a fragment of Cerebral Dopamine Derived Neurotrophic Factor (CDNF). Although neurotrophic factors pose potentially promising routes to dopamine neuron regrowth and disease-modification, due to their size and administration, they require invasive neurosurgery which limits their future feasibility as a treatment. This project looked to see if a fragment of CDNF (C-CDNF) may be able to exert a comparable effect whilst requiring systemic, non-invasive delivery. This work successfully showed that C-CDNF can access the brain in pre-clinical models of Parkinson's. Further work will be needed, however, to determine if peripheral administration of neurotrophic factors will be suitable for people with Parkinson's.

Lõhelaid, H. et al. (2024) CDNF and ER Stress: Pharmacology and therapeutic possibilities. Pharmacology & Therapeutics, 254. https://doi.org/10.1016/j.pharmthera.2024.108594.

Eesmaa, A. et al (2022) CDNF Interacts with ER Chaperones and Requires UPR Sensors to Promote Neuronal Survival. Int. J. Mol. Sci, 23, 9489. https://doi.org/ 10.3390/ijms23169489

CC01: PD-STAT Post Hoc Analysis
Prof Victoria Allgar, University of Plymouth

Prof Allgar conducted a post hoc analysis of the data collected in a Phase 2 trial of simvastatin in Parkinson's. The trial, led by Prof Camille Carroll, involved more than 230 participants and was initiated in 2014 after simvastatin had been prioritised by the iLCT Committee. The trial did not meet its primary outcome however some interesting results were obtained and prompted this further analysis. These learnings will shed light on both the future of simvastatin and similar drugs in regards to Parkinson's but also impact future clinical trials to continually ensure these studies have the highest chance of success.

Appendix 3. McFarthing et al, 2024