COHORT SCIENCE

FULL/LONG TITLE OF THE STUDY

An integrated clinical research platform and 'next generation registry' in patients with Parkinson's Disease

SHORT STUDY TITLE / ACRONYM

AccessPD: A Next Generation Registry in Parkinson's Disease

PROTOCOL VERSION NUMBER AND DATE

Version: 2.0

Date: 14 May 2025

SPONSORS:	Cohort Science Ltd
FUNDERS:	Cohort Science Ltd

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the chief investigator agrees to conduct the study in accordance with the current Good Clinical Practice (GCP) regulations and in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, 21 Code of Federal Regulations (CFR) Parts 11, 50, 54, and 56, the Sponsor's standard operating procedures and other regulatory requirements. Any changes in procedure will only be made if necessary to eliminate immediate hazards and/or to protect the safety, rights, or welfare of participants.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

I agree to keep records on all subject information collected during the study in accordance with the current GCP, local and national regulations.

For and on behalf of the Study Sponsor:

Signature:
.....

Date:
...../...../.....

Name: Anil S Jina, MD

Position: Secretary, Cohort Science Ltd

Chief Investigator:

Signature:

.....

Date:

.....

Name: Dr Alastair Noyce BMedSci, MB BS MSc MRCP PhD FHEA

Position(s):
Professor in Neurology and Neuroepidemiology, Queen Mary University London (QMUL)

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
AccessPD protocol	22-May-2022	Initial version 1.6
AccessPD protocol	14-May-2025	Version 2.0 ● Expanded background and rationale to emphasise the importance of including atypical parkinsonian syndromes (e.g. MSA, PSP, CBS). ● Introduced patient and caregiver interviews as a new data collection method. ● Expanded clinical dataset to include blood tests, imaging, and extended family/social history. ● Broadened use of Patient-Reported Outcome Measures (PROMs), including mortality and hospitalisation. ● Introduced structured classification of sub-studies (Types A, B, and C) with defined governance. ● Enhanced DNA collection procedures and compliance with GDPR and HTA regulations. ● Updated recruitment criteria and expanded patient sampling network. ● Refined risk assessment and implemented strengthened data security measures. ● Revised governance structure with updated committee membership. ● Improved overall protocol clarity, data protection detail, and alignment with GCP/GDPR standards.

LIST of CONTENTS

KEY REGISTRY CONTACTS

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Committees	**AccessPD executive committee:** Principal Investigator: Dr Alastair Noyce Cohort Science representative: Dr Anil Jina uMed Representative: Dr Matthew Wilson Primary Care representative: Dr. Vijaykumar Elango Patient Representative – Mr Andrew Wilkings Industry Representative - TBC

REGISTRY SUMMARY

Registry Title	An integrated clinical research platform and 'next generation registry' in patients with Parkinson's Disease
Internal ref. no. (or short title)	AccessPD: A Next Generation Registry in Parkinson's Disease
Study Design	Remote, longitudinal, observational study Research database and registry Integrated clinical research platform
Study Participants	Patients with a coded diagnosis of Parkinson's Disease or parkinsonism (e.g.progressive supranuclear palsy, multiple system atrophy, etc) +/- additional prescription data in primary care data.
Planned Size of Sample	No upper limit
Follow up duration	20 years
Planned Study Period	20 years
Research Question/Aim(s)	1) To build a registry of participants with a diagnosis of Parkinson's Disease or parkinsonism to access new research opportunities. 2) To create a core clinical dataset including questionnaire data, genetic and other linked clinical data. 3) To improve equitable access to Parkinson's Disease or parkinsonism research opportunities.

FUNDING AND SUPPORT IN-KIND

FUNDER(S)	**FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN**
Cohort Science Ltd 8 Warner Yard, London, EC1R 5EY Email: info@cohort.science Phone: +44 (0) 2033 030329	Sole funder of registry

LIST OF ABBREVIATIONS

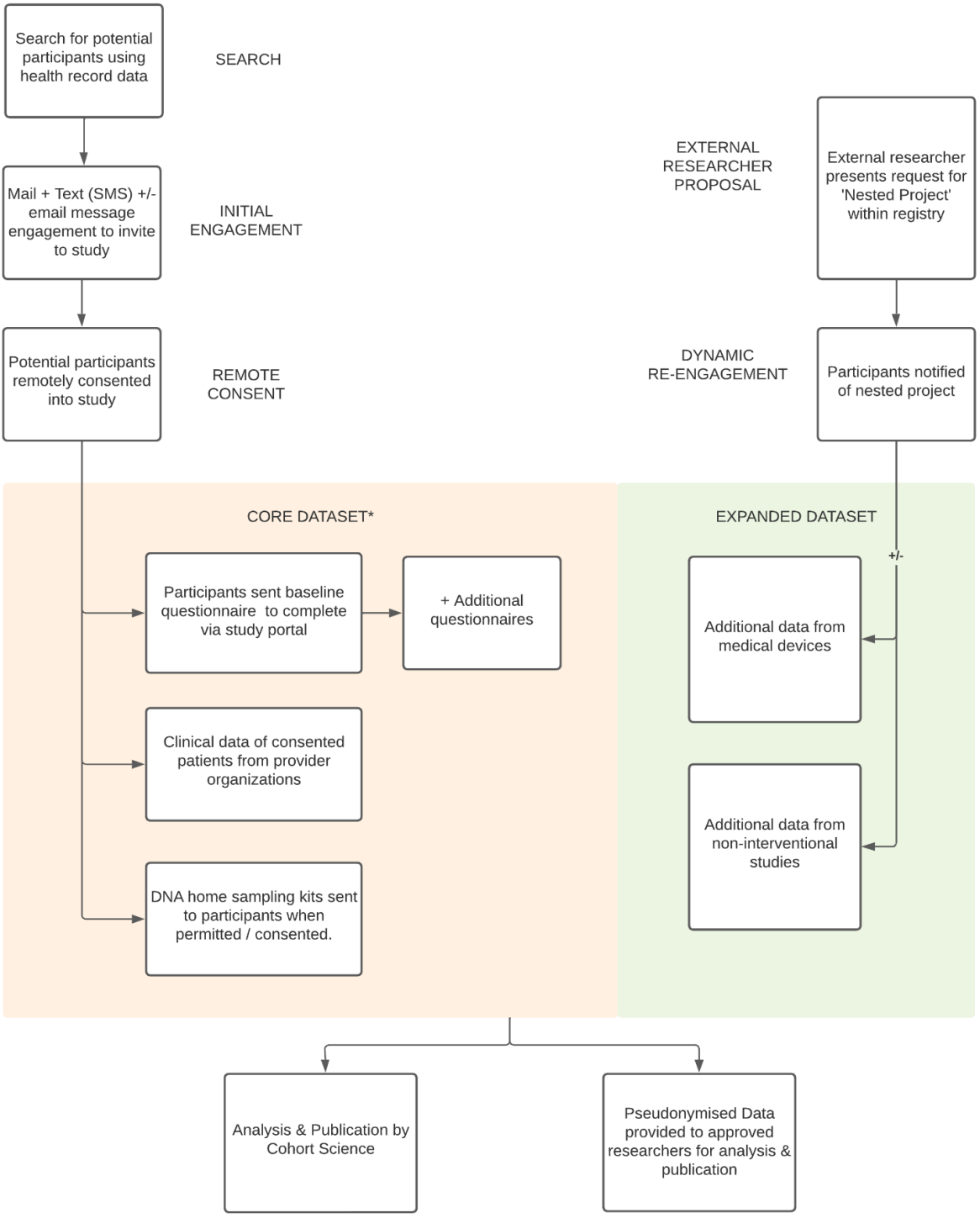
Table 1. List of abbreviations and definition of terms

Abbreviation	Definition
CCD	Core Clinical Dataset
GCLP	Good Clinical Laboratory Practice
CS	Cohort Science
DPA	Data Processing Agreement
DSA	Data Sharing Agreement
EHR	Electronic Health Record
FAQ	Frequently Asked Questions
GCP	Good Clinical Practice
GP	General Practitioner
HCI	Healthcare Institution (GP Practice(s), Hospital)
HCP	Healthcare Provider (GP)
ICF	Informed Consent Form
ICH	International Council on Harmonisation
NHS	National Health Service
PCP	Primary Care Physician
PD	Parkinson's Disease
CI	Chief Investigator
PPI	Patient and Public Involvement
PRO	Patient Reported Outcome
REC	Research Ethics Committee
SMS	Short Messaging Service (i.e. text message)
SOP	Standard Operating Procedure

KEY WORDS

Parkinson's Disease, registry, research database, tissue bank, observational studies, clinical trials, medical devices

REGISTRY FLOW CHART (Figure 1)



REGISTRY PROTOCOL

An integrated clinical research platform and 'next generation registry' in patients with an Parkinson's Disease

1. BACKGROUND

Parkinson's Disease (PD) is the second most common neurodegenerative disease worldwide after Alzheimer's Disease. Evidence from the Global Burden of Disease Study suggests that it may be the fastest-growing neurological disorder worldwide[1]. Risk factors for PD include genetic determinants, environmental risk factors (e.g. pesticide exposure and head trauma), and comorbidities (e.g. type 2 diabetes)[2–4]. However, there is much more work to be done to understand the determinants of PD risk and progression. The clinical course of PD has been well studied in some patient groups, but not all[5]. As with most common diseases, most of the investigation into PD has been undertaken in affluent, White populations residing in Europe and North America. Underrepresented ethnic groups and people living in areas of high deprivation have been systematically under-recruited[6].

Other forms of parkinsonism, including atypical variants such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal syndrome (CBS), share overlapping features with PD, particularly in the early stages, leading to frequent misdiagnosis. These conditions are typically more aggressive, have distinct pathophysiologies, and are even more poorly understood than PD[7–9]. Inclusion of individuals with atypical parkinsonism in research is essential to improve diagnostic accuracy, characterise disease-specific progression patterns, and develop targeted interventions.

Previous registries for Parkinson's Disease, as well as other disease areas, have been limited in their utility as a result of several factors including:

Previously studies have been limited in their utility by, amongst other factors:

a. Representation within the registry population: As described above, many registries are not representative of the true population affected by the disease.
b. Sustainability: The manual tasks undertaken by sites associated with recruiting to and maintaining a registry are often prohibitive to creating a large and comprehensive registry dataset that has the power to undertake meaningful subgroup analyses.
c. Re-engagement: The challenges of re-identification and re-engagement of participants at scale further limits the ability to collect additional data and consent into external studies.

Here we outline a protocol for a 'next generation registry' for patients at risk of or with a diagnosis of Parkinson's Disease or other forms of parkinsonism (including MSA, PSP, and CBS) recorded in primary care, henceforth referred to as AccessPD. This registry is optimised for delivery using a research technology platform that has already deployed across a large number of GP practices in England, allowing the issues identified with traditional registry models to be mitigated. The registry will be able to provide a platform for research and for monitoring health outcomes via linkage to health records and to data captured from patients at home. This will act as a much needed catalyst for implementation research.

2. RATIONALE

The main aim of this project is to develop a 'next generation registry' (a longitudinal, observational, fully remote study utilising technology to collect both electronic clinical records and patient-reported outcomes) for participants with PD and other forms of parkinsonism. The fully remote and observational study will be used to build a cohort of participants with PD, MSA, PSP, and related

conditions for longitudinal study of these populations. This cohort can also be involved in further research opportunities with additional consent, including (medical) device studies and clinical trials of investigational or approved medicinal products.

Through consultation with patients and patient organisations, we recognise the limitations of the current methods of recruitment to clinical research studies. These limitations lead to selection bias and inadequate generalisability of data, as well as poor practice around consent and data handling. Through AccessPD, participants with a diagnosis of PD or other parkinsonian syndromes will be approached remotely and invited to consent to join a disease-specific research registry.

This approach has the following advantages:

a) **Fairness** – By directly approaching patients on behalf of their recognized provider, AccessPD will seek to include all patients with an PD diagnosis, not just those who are treated by research-driven physicians or those being seen at tertiary academic medical centres. The uMed platform can also target and customise outreach to minority populations, ensuring that the study dataset better reflects the overall population of PD patients.

b) **Efficiency and cost** – by identifying potential participants via electronic clinical records, a huge volume of data can be used to select participants for studies with precision and populate research databases, reducing the 'human' effort and costs that are currently required (either by the participant or researcher). Participation accruals will become automated and research data shared across studies (with express consent) so that questionnaires and demographic information does not need to be completed repeatedly if participants are taking part in multiple studies.

c) **Scale** – the registry will recruit prospectively and remotely, enabling more patients to register over time and for the size of the resource to grow. As the process of identification, engagement and consent into AccessPD is automated and utilising remote technology on behalf of participating GPs, the rate of recruitment can be substantially increased in comparison to other observational studies.

d) **Control** – participants will be given full control over how their data is used and the studies in which they wish to participate.

3. THEORETICAL FRAMEWORK

Healthcare providers and other bodies face significant practical, legal and ethical challenges when leveraging patient data assets for direct patient care, as well as secondary use for research. A key unmet need is the facility to allow third parties (e.g., research teams) other than a patient's regular healthcare provider to target, engage and monitor specific sub-groups of patients without burdening clinical staff.

The uMed platform acts on behalf of the patient's healthcare provider to automate the process of conveying engagements to specific patient groups, and collating data for third parties, but ONLY when appropriate authority has been sought and obtained from the patient's healthcare provider and – where necessary – the individual patient.

The current model of participant recruitment is through the type of healthcare organisations with which Umedeor has partnered. Recruitment therefore depends on clinician willingness to have their patients involved in research (bias at the clinician level) and finite site selection due to resource limitation (a

further source of bias). By engaging patients directly, much of this bias is removed and the result is improved access to research opportunities in an equitable manner.

Recognising the need for transparency and accountability, Umedeor created a subsidiary company (Cohort Science Ltd) to act as the registry sponsor and funder for AccessPD. This allows clear separation of the responsibilities and data within the registry workflow.

Umedeor Ltd is a research enabler and service provider to healthcare providers/organisations within the Umedeor network, using the uMed technology platform. Umedeor has access to participant identifiable data through a data processing agreement (DPA) with Healthcare Providers.

Cohort Science (CS) is the registry sponsor and manager of the registry and associated datasets. CS manages the registry dataset and has access only to the data provided by participants that have consented to join AccessPD. CS will provide services to facilitate access and analysis of registry data for external researchers.

AccessPD leverages the uMed technology platform to support the targeted engagement of potential research participants on behalf of the Healthcare Provider (HCP).

Cohort Science (sponsor and data controller) will engage with Umedeor (data processor) through a signed services agreement. Umedeor also acts as a data processor for HCPs, that are in turn data controllers for data held at their practices.

A Research Tissue Bank Participation Agreement between the HCP and Umedeor, will enable the contact with specific groups of patients based on searches of the medical record data held by their HCP (see Appendix 2).

The uMed platform has been successfully used in a range of different studies to support recruitment and remote consent of participants on behalf of HCP's. Through this model, AccessPD will be able to overcome some of the key challenges that are usually associated with conducting a large-scale observational research program, without compromising well- established registry governance, as well as maintaining the highest standards for participant control over use of their data. AccessPD will serve as an example of how registries can be created at scale without placing burden on an already stretched healthcare delivery system. Simultaneously AccessPD will allow the research community to better understand the natural history of the disease and use the 'next generation registry' as a platform to rapidly re-engage participants in order to test new hypotheses and develop new therapies.

A summary of the data protection provisions and governance workflow for AccessPD can be found in **section 9.**

The intent of AccessPD is to create a 'next generation registry' that collects a core clinical set of data from consented patients (AccessPD Core Clinical Dataset [CCD]), consisting of clinical data from their Electronic Health Records (EHR) and relevant Patient Reported Outcomes (PRO) and other information obtained via questionnaires. Umedeor ensures patient identifiable information is always separated from health data via an encrypted layer which prevents complete patient records from being inappropriately accessed. Depending on the contracts agreements between different parties, data will be shared either anonymised or pseudonymised (see Appendix 2).

It will also bring research opportunities to patients with which they can participate. Decisions regarding the ongoing conduct of the study, inclusion of new research opportunities (sub-studies and other research projects), data and participant access requests, manuscript writing and dissemination of results will be taken by the AccessPD Management Committee.

3.1. Open Access to the Core Clinical Data

The CCD will be made openly available to any academic researcher providing their credentials as a researcher and project proposals are approved by the AccessPD Management Committee. Access to the registry dataset will not be unduly restricted and the AccessPD Management Committee must provide written response to any researcher who has been denied access, stating the reasons access has not been granted.

3.2. Sub-studies and Research Projects

Academic and commercial research teams may submit proposals for sub-studies and other research projects to the AccessPD Management Committee for their review.

These sub-studies and research projects are divided into 3 categories:

- Type A: utilise the existing pseudonymised CCD as outlined in the existing protocol.
- Type B: require data collection beyond the existing pseudonymised CCD, but are included in the existing protocol.
- Type C: require data collection beyond the existing pseudonymised CCD, but are not included in the existing protocol. These would require a protocol amendment and updated ethics committee approval.

Where participants are included in such a sub-study or research project, they will be proactively informed by text message and/or email about the nature of the project. Depending on the type of sub-study or research project being undertaken, this may require the participant to explicitly opt-out (Type A), opt-in (Type B) or re-consent (Type C).

Further details of the governance model for different types of sub-studies and research projects can be found in **Appendix 1**.

Any clinical trials or other interventional studies using participants identified through AccessPD will be conducted as standalone trials with separate protocols and will undertake independent ethics committee review prior to commencement.

Appendix 2: Schematic of stakeholders involved in AccessPD.

4. ROLES AND RESPONSIBILITIES

4.1. Study Sponsor

Cohort Science Ltd is the sole sponsor and funder of AccessPD.

4.2. Registry Management Committee

After initial setup, the AccessPD Management Committee will control the final decisions about the conduct of the registry, the inclusion of sub-study and research projects, data analysis and interpretation, manuscript writing and dissemination of results. Applications to view and/or process data from AccessPD will be made directly to the AccessPD Management Committee. Applications must state the reason for the request and the expected outcome(s) of data use. Applications will be reviewed and a decision communicated within 30 days. Reasonable requests for access will not

usually be declined. Data will be shared in a GDPR compliant manner. Initially this will be an anonymised, password protected CSV file transferred via an SFTP secure download or secure access to the uMed platform. In time, we anticipate that data access will be through a dedicated analytics platform. Use of data will be governed by a data use agreement which will capture the purpose and duration of data use, and will be signed by the applicants.

The proposed members of the Management Committee are:

- Chief Investigator: Dr Alastair Noyce
- Cohort Science: Anil S Jina, MB BCh
- Umedeor representative: Matt Wilson, MB BCh
- Primary Care representative: Vijaykumar Elango, MB BCh MRCGP
- Participant representative: Mr Andrew Wilkings
- Industry representative: TBC

4.3. Protocol Contributors

- Chief Investigator: Dr Alastair Noyce
- Cohort Science Ltd: Anil S Jina, MD

5. RESEARCH QUESTION/AIM(S)

The principal **aim** of this project is to develop a new platform for research (described throughout as a 'next generation registry' and called AccessPD), which will establish a core clinical dataset for PD and help streamline widespread, equitable access to additional research opportunities for patients with PD.

5.1. Objectives

a) To establish a new integrated clinical research platform/'next generation registry' for PD.

b) To provide information, obtain consent and recruit patients to the AccessPD platform.

c) To collect a core clinical set of data from consented patients (AccessPD Core Clinical Dataset [CCD]), which would consist of clinical data from their EHR and relevant PRO's and other information obtained via questionnaires.

d) To link the platform to other sub-studies and research projects and offer these new opportunities to participants who are registered with AccessPD. Sub-studies and research projects may require protocol amendments and/or additional ethics committee approval (see Section 3.2).

e) To develop a notification system for clinicians about potential patient participation in additional research. Additional research may be conducted under separate protocols with separate ethics committee approvals.

5.2. Outcome

The main outcome of this project is to build an engaged and active group of participants registered with the AccessPD platform, contributing to the AccessPD CCD, who are also exposed to a range of additional research opportunities, which will streamline progress in PD research and drive better outcomes for patients.

6. REGISTRY DESIGN and METHODS of DATA COLLECTION and DATA ANALYSIS

Potential participants will be identified from EHR according to the participant inclusion and exclusion criteria outlined below (Section 8.1). The initial contact will be via short message service (SMS/text) sent by Umedeor on behalf of the patient's recognized healthcare provider (see figure 1), which will invite potential participants to view information about AccessPD in their smartphone or computer browser. Potential participants may also receive a letter sent by Umedeor as a precursor to receiving SMS communications about AccessPD.

Information will be presented about the aims of the registry and steps required to participate, which include volunteering consent to enrol with the registry and expressing willingness to be approached for additional research opportunities.

AccessPD will invite participants to complete PRO's and other medical questionnaires to generate a set of core clinical data for research (AccessPD CCD).

A list of initial PRO's and questions is provided below. Additional PRO's and questionnaires which may be administered in the future will require protocol amendments and/or ethics committee approval.

6.1. Clinical Assessment

Where available, all participants recruited will have the following information extracted from their EHR or answer questions to provide more details:

- Demographics (Age, sex, ethnic group, race, education (level/years))
- Comorbidities (including acid reflux)
- Vital signs (weight, height, blood pressure, heart rate, oxygen saturation)
- Routinely collected blood test results (such as liver, renal and thyroid functions, glucose, HbA1c, haematology tests, troponin and N-terminal pro B-type natriuretic peptide etc.)
- Current and previous medications
- Date of symptom onset and first symptom
- Specific diagnosis
- Date of diagnosis and setting (primary or secondary care)
- Name of specialist and/or treatment centre
- Other personal medical history
- Family medical history (including genetic conditions)
- Social history (including occupation, diet, physical activity, smoking, alternative medicine, exposure to pesticides and insecticides, postcode, Townsend Score of social deprivation)
- Previous imaging or diagnostic test results (e.g. ECHO, cardiac catheterisation, ECG, x-rays, CT scans, etc.)
- Other ad-hoc questions related to experience of cardiac complications, its treatment and participant reported outcomes
- Other outcome measures which will be included (see **Appendix 3**):
    - Mortality

- Hospitalisation rate
- Progression of disease

It is anticipated that many of these data fields will be populated by record linkage. The maximum completion time for questionnaires administered at any one time is not expected to exceed 30 minutes.

Depending on the sub-studies and research projects that are linked to AccessPD, participants may be invited to complete additional scales and questionnaires. These may be self-reported or involve remote or in-person clinical assessment. A list of potential clinical scales is provided in **Appendix 3.**

After enrollment, participants may be invited to participate in additional research studies relating to AccessPD. These studies may be initiated by Umedeor, their academic partners, or independent academic and/or commercial entities. Participants will retain full control over their participation and how their data is used. Additional research will be conducted under a protocol amendment (or a separate protocol) and updated ethics committee approval, if it is not covered in this protocol.

Examples of additional research opportunities include:

1) **Longitudinal or cross-sectional observational studies**

- Questionnaires about PD status administered periodically
- Questionnaires about PD risk factors
- Objective tests such as ECG, ECHO.
- Virtual or in-person clinical assessments

2) **Medical device studies** – medical devices for measuring symptoms of PD or providing treatment.

3) **Clinical trials** of approved or investigational medicinal products (using a traditional or decentralised model).

4) **DNA collection and analysis**

Participants may be invited to submit a saliva or blood sample for DNA extraction and analysis. An at-home saliva sample collection kit will be dispatched in the mail to participants that consent to saliva collection and returned to a central lab for DNA extraction and storage. Blood samples would be taken at a participant's healthcare centre and analysed by an accredited laboratory with relevant licences (e.g HTA licence where required).

Analysis (genotyping and/or sequencing) will take place at an approved laboratory (UK or international) that meets GDPR requirements. Saliva is covered by the Human Tissue Act 2004 (HTA) but DNA falls outside the remit of the HTA and can be shared with explicit consent and when GDPR requirements are met. DNA may be shared with approved collaborators (academic and commercial), in the UK or outside the UK (worldwide) to further understanding of PD. Genotyping and/or sequencing data and clinical data may be shared in aggregated or de-aggregated forms, with approved collaborators (academic and commercial), in the UK or outside the UK (worldwide) to further understanding of PD. Researchers receiving samples and/or data must have a written usage agreement. Samples will be stored for as long as deemed useful for research purposes.

7. REGISTRY SETTING

Most engagement with participants will happen remotely and online. The initial approach will be made by an SMS message sent by Umedeor on behalf of the patient's HCP (+/- written material sent via mail), after identifying patients with a diagnosis of PD from electronic medical records. Registration, information provision, consent to participate and research activities will all be managed and accessed via the online AccessPD portal.

8. SAMPLE AND RECRUITMENT

8.1. Eligibility Criteria

8.1.1. Inclusion criteria

The principal goals of this project are to establish a core clinical dataset for PD and to improve representativeness in PD research. Hence the inclusion criteria are:

- All patients with a coded diagnosis of PD and/or parkinsonism (e.g.progressive supranuclear palsy, multiple system atrophy, etc) +/- additional prescription data (see Appendix 9) in primary care data.
- Aged >18 years old.
- Identified through a HCP participating in AccessPD.
- Able to provide consent to participate.

8.1.2. Exclusion criteria

- Patients who have recorded a preference in their medical record that they do not wish to be considered for research or contacted regarding research opportunities.
- Patients who have recorded a preference not to share data for research (based on the NHS Digital National Opt out database).
- Patients who are in palative care, on the death register or have dementia are not identifed for engagement during EHR searches as part of the uMed exclusion criteria.

8.2. Sampling

Through its network of agreements with NHS primary care providers, uMed has access to 3 million (as of May 2023) patients' primary care electronic health records in the UK and a mandate to approach them to promote research opportunities.

All patients with a coded diagnosis of PD (defined above) will be offered the chance to join the registry and proceed according to the terms of their consent.

8.2.1. Size of sample

Due to the aim of the project (i.e. to develop a new platform for research, which will streamline widespread access to research opportunities for patients with PD, whilst improving equitability), the sample size will be as high as possible and is not based on statistical power calculation. We will aim to recruit a similar percentage of patients from each high level diagnostic group and aim to maximise for ethnic, geographic and socio-economic diversity across the recruited population.

8.2.2. Sampling technique

As above, the aim is to offer participation to all patients with a diagnosis of PD identified through a healthcare provider participating in AccessPD within the Umedeor network in the United Kingdom.

8.3. Recruitment

Potential participants will be identified from EHR at GP practices with whom Umedeor have a partnership agreement, based on the inclusion and exclusion criteria above.

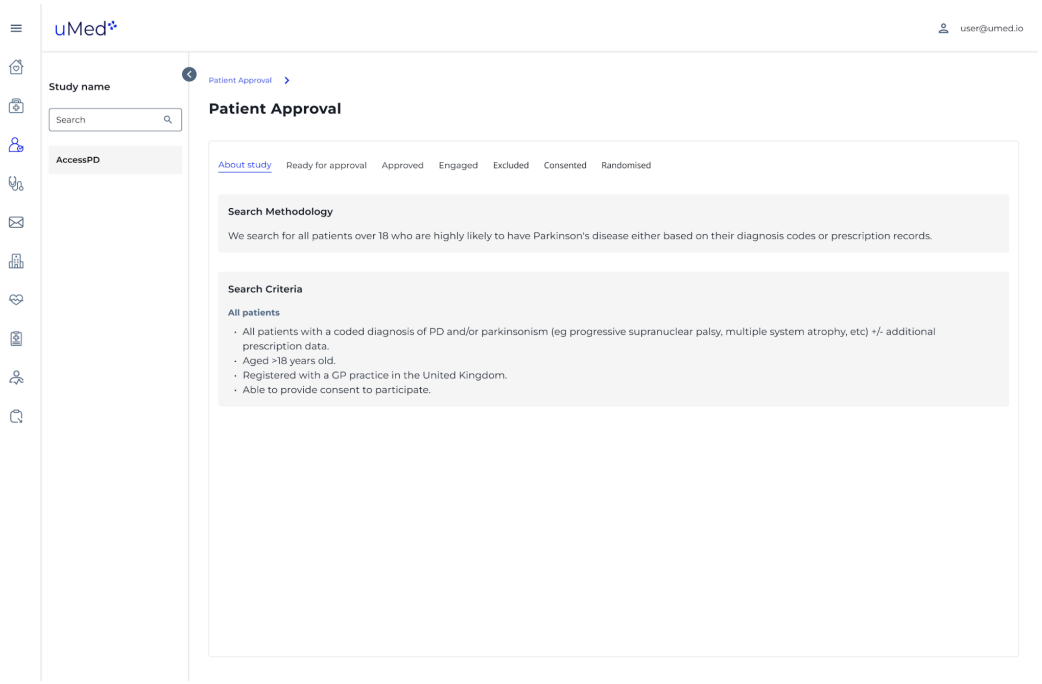
8.3.1. Sample identification

This will involve the following steps:

a) A search will be undertaken to identify potential participants using clinical data from the EHR of HCP's who have agreed to participate in the Umedeor network. This search of clinical data will identify potential participants in line with the inclusion /exclusion described above.

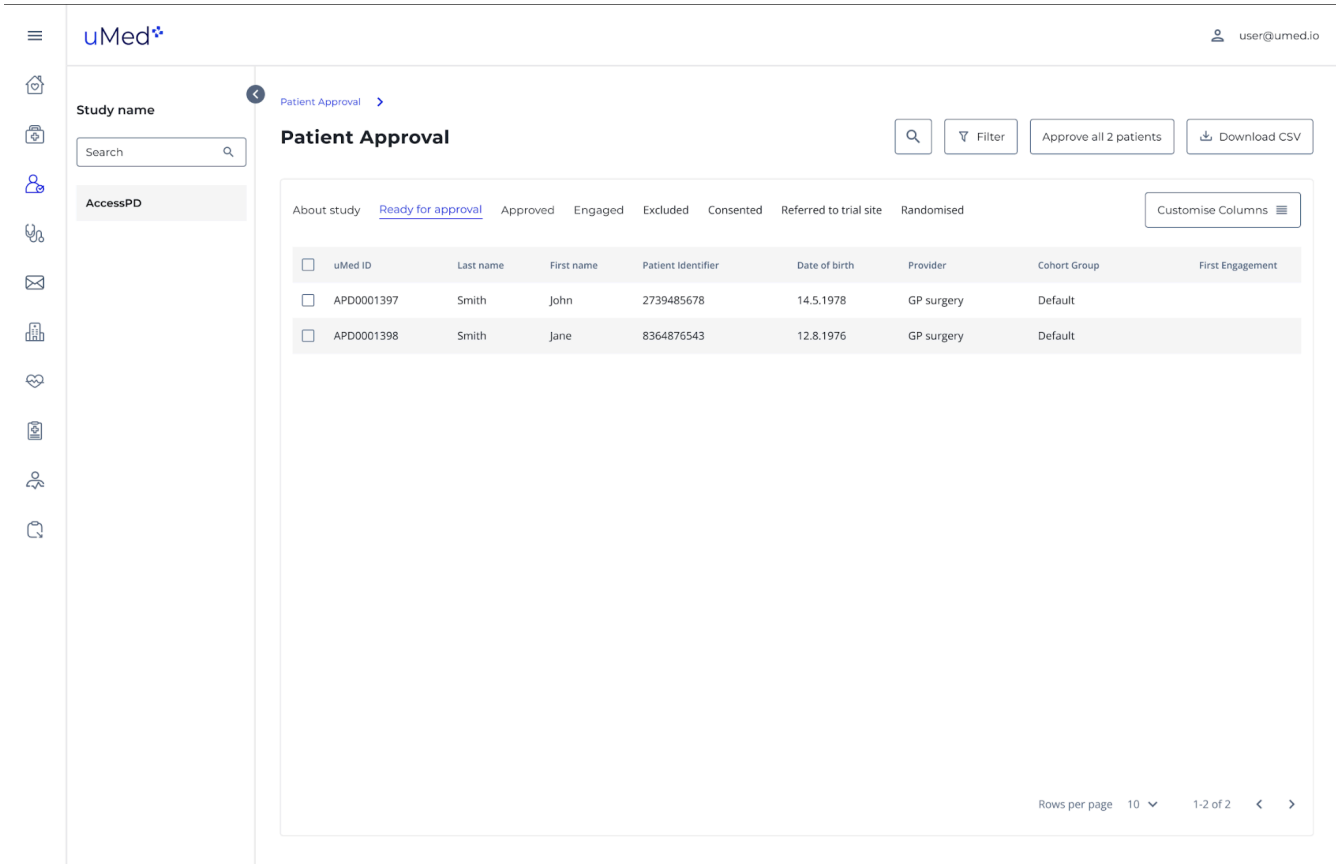
b) When potential participants have been identified, HCP's will be notified via the uMed platform and presented with all relevant information about AccessPD (illustrative example of HCP user interface provided below in Figure 3).

Figure 3: HCP User Interface Example



c) HCP's will be able to sign clinical registry agreements and supporting registry documentation via the user interface using integration with DocuSign.

d) Once onboarded, HCP's will be able to review the list of potential participants identified via the clinical data search and exclude any patients they believe should not be contacted for the registry.



a) Once approved by their HCP, potential participants will be automatically contacted via mail, SMS, and/or email and provided a participant specific link to sign up for AccessPD.

8.3.2. Consent

In accordance with relevant regulations, an informed consent agreement explaining the procedures and requirements of the study, details on how individuals' confidentiality will be maintained, and potential hazards/risks, will be presented to potential participants. Potential participants will be shown a short video along with a clickable participant information leaflet, a list of frequently asked questions (FAQs) and contact details (email, web-form) in case of questions. They will then view the consent form which includes a list of statements, including a request for consent to linkage of data to electronic health records and relevant datasets held by NHS England (e.g. HES). They will select the statements that they agree to and submit these.

After consenting, consented participants will be able to complete the core clinical data questionnaires outlined above and view other research opportunities, including reading relevant registry information and, if interested, participate in those studies.

The precedent of gathering web-based consent alongside provision of information is well established. Capacity in clinical settings is decision-specific and assumed unless there is evidence to the contrary. It is unlikely that PD patients with loss of capacity to participate in research would be actively responding to SMS messages inviting enrolment in a registry. However, the nature of data being collected and the non-invasiveness of the research undertaken in AccessPD mean that there is minimal risk posed to participants

9. ETHICAL AND REGULATORY CONSIDERATIONS

The Health Research Authority has a UK Policy Framework for Health and Social Care Research. The Policy Framework begins with an outline of the aspects that contribute to delivering research of the highest quality and to which the HRA is committed. Selected examples are listed below, along with a description of how the AccessPD project has taken these into consideration.

Regulatory/ethical consideration	**AccessPD**
Patients, service users and the public are given, and take, the opportunity to participate in health and social care research and to get involved in design, management, conduct & dissemination.	Patients, patient representatives and patient advocacy groups will be involved in the project design, scoping and priority setting. A PPI group is planned before commencement of AccessPD and will continue to advise as the project progresses.
Safer, more efficient or more effective treatments, care and other services are developed and tested through ethical and scientifically sound research for the benefit of patients, service users and the public.	AccessPD will enhance access for patients to research opportunities and the PD research community to a unique dataset that combines clinical data, participant reported data and biosamples. Together this will drive better understanding of aetiology, manifestation, progression and potential therapeutic targets, as well as efficient recruitment for clinical trials.
Ensure that study populations better reflect the patient populations who could ultimately benefit from the research in clinical practice.	AccessPD will enhance access for patients to research opportunities, and make it easier for researchers to reach out to underserved populations. The use of clinical data also promotes more efficient recruitment of a diverse population and supports identification of participants for whom traditional referral centres are not accessible.

Researchers find it straightforward to do high-quality, ethical research.	AccessPD will dramatically improve efficiency when it comes to identifying eligible participants for research and offering the opportunity to participants in a highly equitable manner.
Industry sees the UK as a great place to do health and social care research, and increases its investment for the benefit of patients and service users.	Industry-led and academic-led research projects will be offered in the platform, increasing efficiency and breadth of opportunities, with increasing investment from those stakeholders.
Money from foundations and other research funders goes into carrying out research, not into navigating burdensome bureaucracy or duplicating previous work.	The AccessPD model creates a platform which allows an ever growing dataset to be created and accessed by researchers. In doing so this dramatically reduces the cost and burden associated with creating bespoke programs that still remain the status quo.
Research projects get registered, the data and biosamples they collect can be made available for future analysis, with adequate consent and privacy safeguards, and research findings get published and summarised for those who took part in them.	AccessPD is committed to an open science framework and sets a new standard for privacy safeguards by ensuring a broad based consent for secondary use of registry data is balanced through proactive engagement (and the ability to opt out) of specific secondary use projects. The platform also enables efficient sharing of publications and research summaries with participants.

9.1. Assessment and management of risk

Potential risks that have been identified:

Risk	Describe the source of risk and the nature of the potential impact on individuals. Include associated compliance and corporate risks as necessary.	Likelihood	Impact	Overall Risk
1	External parties attempt to access data with malicious intent.	Low	Major	3
2	Malicious action by uMed employees to access, alter, or exploit data held on the registry system.	Low	Major	3
3	Patients receive an unwanted solicitation to engage in research.	Medium	Significant	2

4	A participant's health data is shared with a third-party organization using the registry system against their expectations or wishes.	Medium	Significant	2
5	A participant is misidentified in communications leading to preferences and/or responses being associated with another record.	Medium	Significant	2
6	A third-party research group (e.g., a pharmaceutical company) that accesses sensitive data via the registry system utilizes this data for purposes beyond those stated in the data-sharing agreement.	Low	Major	3
7	Participant preferences listed in the registry conflict with those held by the participant's healthcare institution.	Medium	Minor	2
8	uMed fails to meet compliance requirements for information and security governance.	Low	Major	3
9	uMed becomes insolvent while holding sensitive data within the registry system.	Low	Significant	2
10	A change in privacy/data legislation invalidates registry system processes.	Low	Significant	2

Mitigating Actions

Risk	Options to reduce or eliminate risk	Effect on risk	Residual risk	Measure approved
1	Data is encrypted at rest and hosted in a certified Amazon Web Service (AWS) environment in line with or exceeding the standards set by NHS England. Penetration testing and external security certification reports are available on request	Reduced	Low	Yes

2	The registry system has implemented SOPs to address this risk including: ● Confidentiality Statements acknowledged by employees ● Prospective employee vetting ● Password Management SOP ● Assignment of unique identifier to employees to allow for tracking of access ● Two-factor authentication is in place to verify employee access. ● Actions on Employment Termination SOP ● An access control policy is in place as part of the acceptable use policy to manage the access of participants identifiable information and sensitive data.	Reduced	Low	Yes
3	All correspondence makes clear to the subject why they are being contacted and how to change preferences to prevent unwanted further correspondence.	Eliminated	Low	Yes
4	When using the registry system, participants associated with a specific DSA will be informed even when sharing does not require consent as a legal basis. This allows participants to 'opt-out' of a given DSA.	Reduced	Low	Yes
5	The participant's identity will be confirmed before any consent is obtained. This is achieved by asking the participant to confirm the DOB, which is cross referenced with the DOB held against the record associated with the contact information in question. This contact information is obtained from the *HCI,* which supports another implicit layer of identity verification.	Reduced	Low	Yes
6	If the registry system is used to facilitate data sharing with a third party, access is only granted once the data sharing agreement is in place. Audit logs give an immutable record of activity and any access by named individuals within a 3rd party. E.g., DAs, etc. Breach of this could result in legal action.	Reduced/ Accepted	Low	Yes
7	The registry system will record any participants who opt out of receiving contact and will inform the HCI.	Reduced	Low	Yes
8	In the event uMed becomes insolvent, all data created from participant engagement, including metadata and logs, will be returned to the provider organizations associated with their participant population. All copies of sensitive and personal data will be destroyed and access granted to *HCIs* and/or independent auditors to demonstrate this.	Eliminated	Low	Yes

9	uMed continuously reviews current and planned data legislation. If a change in data legislation is likely to affect uMed operations, then this will be highlighted alongside the mitigating measures planned by uMed to ensure ongoing compliance.	Reduced	Low	Yes
10	Policies are in place regarding the final disposal of electronically protected health information and the disposal of hardware/electronic media associated with the storage of such data.	Eliminated	Low	Yes
11	Policies and procedures are in place for responding to an emergency or other occurrence that damages systems that contain electronically protected health information. Procedures supporting data backup and recovery are in place, along with disaster recovery and Business Continuity Plan.	Reduced	Low	Yes

9.2. Potential Benefits

Participants will not benefit directly from being in this research study.

9.3. Research Ethics Committee (REC) and other Regulatory review & reports

Prior to the start of the registry, approval was sought from a REC (researchers should check if they are required to gain a favourable opinion from the UK Health Departments Research Ethics Service NHS REC) for the registry protocol, informed consent forms and other relevant documents e.g. advertisements. In addition:

- Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site.
- All correspondence with the REC will be retained.
- It is the Sponsor's responsibility to produce the annual reports as required.
- The Sponsor will notify the REC of the end of the registry.
- An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the registry is declared ended.
- If the registry is ended prematurely, the Sponsor will notify the REC, including the reasons for the premature termination.
- Within one year after the end of the registry, the Sponsor will submit a final report with the results, including any publications/abstracts, to the REC.

9.4. Regulatory Review & Compliance

Before any site can enrol patients into the registry, the Sponsor will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance. Different arrangements for NHS and non-NHS sites are described as relevant.

For any amendment to the registry, the Sponsor, in agreement with the Chief Investigator, will submit information to the appropriate body for them to issue approval for the amendment. The Sponsor will work with sites (R&D departments at NHS sites as well as the registry delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the registry as amended.

9.5. Amendments

Amendments to the protocol, participant information and consent forms will be made as required, for example, if the nature of information/data being collected from participants were to change. Amendments will be led and coordinated by the sponsor (CS Ltd). The decision about when to make an amendment will be taken by the sponsor, who will also determine whether the amendment is substantial or non-substantial. Amendments will be notified via email to relevant stakeholders and the amendment history (along with all supporting documentation by version number and date) will be retained.

9.6. Patient & Public Involvement Group

AccessPD will undertake regular PPI group consultation to capture broader feedback on the activity taking place within the registry.

A PPI group is currently being convened and a PPI event will be held in the next month for patients with PD, carers and also expert practitioners who support this group of patients. Initially gaining holistic feedback from patients and patient representatives on the protocol, patient information leaflet, patient engagements and study structure. In addition, routine periodic PPI steering groups allow for feedback opportunities. A quarterly newsletter providing patient updates will also be sent to participants, feedback will always be encouraged and welcomed.

9.7. Protocol compliance

This protocol provides a written guide for the conduct of the project. Deviations from the protocol (if they occur) will be recorded by date, alongside a description of the deviation and will be available for audit.

9.8. Data protection and participant confidentiality

Data protection has been a key consideration since the conception of the uMed platform and has been developed further when constructing the AccessPD protocol. For clarity, this section has been split into data protection and participant confidentiality considerations that relate to Umedeor vs those that relate to Cohort Science Ltd.

9.9. Cohort Science Ltd and Umedeor Ltd

Both businesses comply with UK GDPR, the UK Data Protection Act 2018, and the Common Law Duty of Confidentiality. Both businesses are also compliant with the NHS Data Protection & Security Toolkit, the ISO27001:2022 Information Security Management System, and hold a Cyber Essentials Plus certification.

The core principle applied throughout AccessPD is that Umedeor always acts as a data processor on behalf of the investigator sites (GP practices) involved in the registry..

This data processing agreement (aka platform agreement) allows Umedeor to access and utilise EHR data from the practice to provide services to support delivery of studies. Umedeor therefore cannot use or share provider data with any third party without the permission from the GP practice (data controller). Consequently, the uMed platform includes provision for an authorisation workflow to enable the practice to give permission(s) for engagement and/or sharing of data in-line with the AccessPD protocol. This process also ensures that an audit trail is created such that the sponsor is able to confirm all required permissions have been given by each site.

Cohort Science data will be extracted as encrypted files that are sent to AWS S3, and then decrypted and ingested by the CS AWS account.

Further detail can be found in **Appendix 5: Umedeor IG Whitepaper.**

9.10. Health Record Data Security

Umedeor applies the latest cloud-based security principles to ensure that data is held securely on our Amazon Web Service (AWS) infrastructure. In addition to conforming to the standards set by NHS Digital, the uMed platform goes beyond this to create a gold standard for information security of health data. It achieves this by ensuring patient identifiable information is always separated from health data via an encrypted layer which prevents complete patient records from being inappropriately accessed.

Additional information relating to the Umedeor business processes that ensure information security can be found in the Umedeor Information Management Security System documentation which is available on request. DSP Toolkit registration data can be found at:

https://www.dsptoolkit.nhs.uk/OrganisationSearch/8K677

https://www.dsptoolkit.nhs.uk/OrganisationSearch/f2f6l

9.11. Data Retention

As Umedeor provides services to GPs requiring access to GP data, Umedeor holds this data until the data processing agreement between Umedeor and the GP site expires or is terminated.

9.12. Data Encryption & Transmission of Data to Study Sponsor

Umedeor only transfers data to a third party once the data controller and the participant has given permission for the transfer in line with requirements set out in the AccessPD protocol.

The following data must be always encrypted using minimum 2048-bit encryption:

- Data backups - encrypted using high grade secure keys.
- Data in transit uses public/private certificate key pairs for exchange of data.

Any exchange of data with external systems uses unique key pairs per source/destination.

Encryption keys are stored on a separate secure key management system (KMS) that uses FIPS 140-2 validated hardware security modules (HSMs) to generate and protect keys.

Access to private keys is restricted to specific users with appropriate security clearance and access is logged. The Head of Security must approve access requests for any encryption keys.

9.13. Cohort Science Ltd

Prior to transfer of any registry data to Cohort Science (CS), permission of the registry site (data controller) and participant consent will have been sought and obtained in line with the requirements of:

a. The registry protocol.
b. CS - Site clinical trial agreement.
c. Umedeor - GP data processing agreement.

All data transferred to CS by Umedeor on behalf of the registry site will be pseudonymised[1] prior to transfer. All participant identifiers will be removed and an encrypted pseudo-ID will be used that can be passed back to Umedeor if participant re-identification / re-engagement was required.

All registry data will be held in CS AWS infrastructure and no individual will have common access to CS as well as Umedeor data infrastructure.

All transfers between the Umedeor and CS will be logged and reports made available to external auditors on request. All access to CS datasets will also be logged with access restricted only to the CS research team and external researchers approved by the registry Management Committee.

9.14. Data Retention

In line with MRC guidance, registry data will be retained for a period of 20 years after the registry has been completed.

9.15. Access to the registry dataset

AccessPD aims to balance the goals of ‘open science’ alongside creating a sustainable registry model that incentivises academic and commercial researchers to engage with the registry and develop new ideas, diagnostics and therapies that can improve the lives of patients with PD.

A: Any access to AccessPD data or samples will require approval by the registry Management Committee *(see* ***Appendix 8****)*

B: Access to DNA samples

[1] Pseudonymisation refers to techniques that replace, remove or transform information that identifies individuals, and keep that information separate. Umedeor carries out pseudonymisation in accordance with Article 4(5) of the UK GDPR

Access to samples may be provided to researchers for the purpose of genotyping/sequencing. It is a requirement that data from this analysis of DNA will be provided back to Cohort Science and integrated into the Core Clinical Dataset. Researchers requesting access to DNA samples will be required to provide evidence to the registry Management Committee of affiliation to a bona fide research institution that has the requisite governance in place to manage DNA samples and the resulting genotype/sequencing data.

C: Open Access to Core Clinical Data

All academic researchers will be provided access to the CCD once their credentials have been validated and a description of the intended project that will use the registry data has been provided to the registry Management Committee. The AccessPD CCD includes:

a. Baseline and scheduled questionnaire data.
b. Linked clinical health record data.
c. DNA genotype/sequencing data.
d. Any additional data collected as part of a supported registry or sub-studies where the funder of that registry/project has agreed for that data to be included in the open data.

D: Additional data captured under AccessPD protocol

To preserve incentives for industry engagement, Cohort Science or the funders of 'Sub-studies' that capture additional data from registry participants will be able to request that access to this subset of data is restricted to specific users.

Unless exceptional reasons are presented to the registry Management Committee, access to this additional data will not be restricted for more than 1 year after publication. After which, the previously restricted data will be made available as part of the CCD.

Importantly, participants associated with 'sub-studies' will be proactively engaged and presented information explaining who is funding the project and if access to data from this sub-study will be restricted. Participants are given a clear means to then opt out of further engagement with the 'Sub-studies'.

9.16. Subject Withdrawals

Subjects will be advised in the informed consent that they have the right to withdraw from the study at any time without prejudice. In instances where participants want to withdraw their data/biospecimens from the study, the uMed platform has the capability to identify and remove the data linked to specific individuals.

If a participant wishes to withdraw their data/biospecimens from the study, the participant may submit such a request to the study team via phone or email. The study team will make every effort to remove the participant from the registry and have his or her samples destroyed. However, in some cases, it may be impossible to locate and stop such future research on your specific sample if all identifiers were stripped from your sample prior to the sample being provided to other investigators.

10. DISSEMINATION POLICY

10.1. Dissemination policy

- Cohort Science Ltd will manage and be responsible for the pseudonymised CCD.
- Any external researcher wishing to publish based on data from AccessPD will need approval from the registry Management Committee.
- Study protocol will be made available via appropriate web portals (e.g. HRA website, clinicaltrials.org) within 6 months of commencing registry recruitment.
- Participants will automatically be notified of any publication that arises as a result of their participation in AccessPD. This will be achieved using the uMed platform and notifications will be sent via email or SMS in line with the participants' stated preferences. Participants will be provided with a layperson language summary of the publication alongside a link to the article.

10.2. Authorship eligibility guidelines and any intended use of professional writers

Cohort Science and Umedeor will be acknowledged as the sponsor and facilitating technology platform respectively in any publication using registry data.

11. REFERENCES

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12. APPENDICES

Appendix 1: Governance of Sub-studies within AccessPD

Appendix 2: Stakeholder Relationship Schematic

Appendix 3: Questionnaires and scales for 'sub-studies'

Appendix 4: SNOMED-CT codes for Inclusion & Exclusion Criteria

Appendix 5: Umedeor Information Governance White Paper

Appendix 6: Schedule of Activities (Example)

Appendix 7: Previous success with Access-PD

Appendix 8: CS Data access application

Appendix 1: Governance of Sub-studies run within AccessPD

Sub-studies will be categorised into 3 types:

Type A: Sub-studies using the existing pseudonymised study dataset as outlined in the existing protocol.

Type B: Sub-studies requiring additional data collection beyond the existing pseudonymised dataset, which are included in the existing protocol.

Type C: Sub-studies requiring additional data collection beyond the existing pseudonymised dataset, but are not included in the existing protocol. These would require a protocol amendment and updated ethics committee approval.

Type A sub-studies will enable research teams external to AccessPD to access the existing pseudonymised study dataset only. Access will be granted subject to review of the request by the AccessPD Management Committee.

As Type A sub-studies only utilise existing data and consent is already obtained for this secondary use, the participant does not need to opt-in. Umedeor will still proactively engage participants when AccessPD intends to share data with external research teams and participants will be given the opportunity to opt-out for access by specific external researchers.

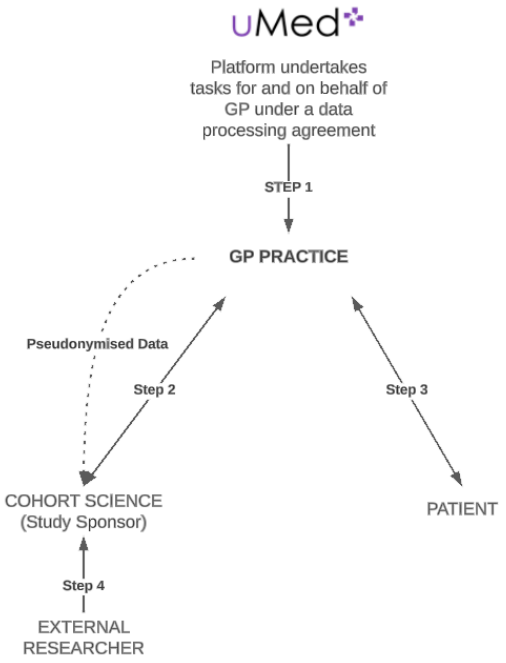
Type B sub-studies are defined as those that will seek to capture additional information which is contained in the protocol, but not included in the core study dataset (e.g. PRO's, questionnaires or observational data collected through in-person or remote visits with the study team). Participants presented with the opportunity to provide additional data will be required to opt-in to such activities. Data will always be pseudonymised prior to access by external researchers. These sub-studies do not require a protocol amendment or ethics committee approval.

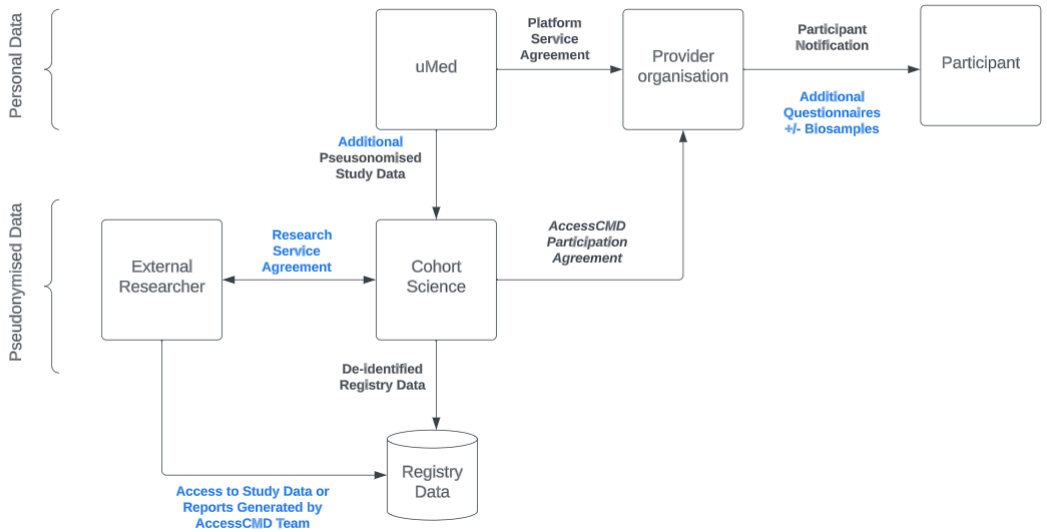
Type C sub-studies allow sub-groups of patients within AccessPD to be recruited for studies designed to collect information not contained in the existing protocol (e.g. additional PRO's, imaging, diagnostics, wearable technologies [NB: any wearable technologies used will only be used for measurement purposes]). These type C sub-studies would be submitted as an amendment to the AccessPD protocol with subsequent ethics committee approval. Participants within AccessPD who wish to engage with the opportunity to be part of Type C sub-studies will be required to re-consent.

Note. Any interventional or clinical drug or medical device studies recruiting participants identified through AccessPD will be conducted as standalone trials with their own protocols and will undertake independent ethics committee review prior to commencement.

Appendix 2: Stakeholder Relationship Schematic

Process Flow:





Step 1:
Umedeor has a data processing agreement with the HCP and a Study Research Tissue Bank

Participation Agreement. This allows Umedeor to undertake tasks including search of health records to identify potential participants and engagement of those potential participants once this list of individuals has been reviewed and approved by the healthcare provider within the uMed platform.

Step 2
The study sponsor (Cohort Science) enters into an agreement with Umedeor to process study specific data agreement with a HCP. Umedeor's technology helps identify suitable healthcare provider sites and supports the providers in completing the relevant study onboarding documents (eg, study agreement)

Step 3
Umedeor, with the approval and on behalf of the provider organisation, will contact potential participants and ask them to enrol in AccessPD. This includes a link to the participant information sheet, information videos and an electronic consent workflow. Umedeor acts on behalf of the provider to automate this outreach via text, email, and letter.

Once consented, the participants will be sent study questionnaires and other data collection (e.g. DNA tests) over several months. Data collected from participants is consolidated with health record data and shared with the study sponsor (Cohort Science) in pseudonymised form.

Step 4
External researchers can engage with AccessPD through 'sub-studies' which enables access for those external researchers to pseudonymised data and additional data collected from subgroups within the AccessPD population to support analyses of specific research questions.

When an external researcher wishes to engage in a sub-study, the pseudo-IDs of relevant participants will be shared with the provider's practice. Acting on behalf of the provider and the sponsor, Umedeor will then reidentify those participants and engage them to collect the additional data required for that sub-study.

All sub-studies that provide access to data and/or samples will need to be approved by the AccessPD Registry Management Committee. Further information on how access is managed can be found in section 8.8 of the protocol.

Appendix 3: Questionnaires and scales for 'sub-studies'

Scales		
Name	**Domain**	**Duration**
MDS Unified Parkinson's Disease Rating Scale 1. Non motor aspects of daily living 2. Motor aspects of daily living 3. Motor examination 4. Motor complications	Multi-domain	30 mins
Unified Multiple System Atrophy Rating Scale (UMSARS)	Multi-domain	30 mins
Hoehn & Yahr scale	Motor severity	5 mins
The Schwab and England ADL (Activities of Daily Living)	Mobility	10 mins
The Barthel Index (BI)	Activities of Daily Living	5 mins
Clinical Impression of Severity Index for PD (CISI-PD)	Severity	5 mins
Non-Motor Symptom Scale	Non-motor symptoms	15 mins
Non-Motor Symptoms Questionnaire	Non-motor symptoms	7 mins
SCOPA-AUT	Autonomic function	15 mins
Hospital Anxiety Depression Scale or similar	Mood	5 mins
Montreal Cognitive Assessment	Cognition	10 mins
RBD screening questionnaire, Epworth Sleepiness Scale	Sleep questionnaires	5-10 mins each
Wearing off assessment	Motor symptoms	<10 mins
PDQ-39 (including PDQ-8)	Quality of life	10 mins
EQ-5D-5L and EQ-5D-5L Visual Analogue Scale	Quality of life	10 mins
MERQ-PD-B or PD-RDU-Q	Environmental Risk factors	10 mins
Kings Pain Scale	Pain	10 mins

Objective tests		
UPSIT smell test (40-item)	Olfaction	20 mins
6-item (PREDICT-PD) smell test	Olfaction	<5 mins
BRAIN test	Motor keyboard tapping task	<5 mins
Selected cognitive tests	Cognition	Varies
Patient and caregiver questionnaires/interviews regarding:		
Patients experience with their disease (signs, symptoms and limitations)		
Patients treatment experience of their disease		
Disease status		
Disease risk factors		
Psychometric interviews ● Concept elicitation interview (CE), participants will be asked about their usual experiences with their disease and its physical and daily life impacts. ● Cognitive debriefing (CD), interview, participants will be asked to review select digital measures of activity and answering follow up questions on the clarity, relevance, and alignment between the measures themselves and the day to day functional impairments they experience. Participants will also be asked how much change in each measure would be meaningful.		

Appendix 4: SNOMED-CT codes for Inclusion

SNOMED Code	Term
49049000	Parkinson's disease
907151000000108	Seen by Parkinson's disease service
862081000000106	Referral to Parkinson's service
924261000000104	Referral to community Parkinson's disease clinical nurse specialist
879471000000102	Referral to community Parkinson's service
515841000000104	History of Parkinson's disease
718685006	Orthostatic hypotension co-occurrent and due to Parkinson's disease
101421000119107	Dementia due to Parkinson's disease
341551000000108	Cerebral degeneration in Parkinson's disease
715345007	Young onset Parkinson disease
230297002	Multiple system atrophy (disorder)
444024002	Multiple system atrophy, cerebellar variant (disorder)
444197004	Multiple system atrophy, Parkinson variant (disorder)

Appendix 5: Umedeor Information Governance White Paper

See accompanying document

Appendix 6: Schedule of Activities (Example)

Procedures	**Visits (insert visit numbers as appropriate)**			
	Screening	**Baseline**	**Every 6 Months**	**Unscheduled**
Informed consent	x			
Demographics (via EHR)		x		
Medical history (via EHR)		x		
Routinely collected blood test results (via EHR)		x	x	
Symptom Questionnaire		x	x	
Patient Reported Outcomes			x	
Supplementary questionnaires/PRO's/clinical outcome measures				x
Contact for participation in 3rd party studies				x

Appendix 7: Previous success with Access-PD

See accompanying document.

Appendix 8: CS Data access application