FULL/LONG TITLE OF THE STUDY

Utility of 3-dimensional gait analysis in reference to clinical assessments to detect significant change after a cerebrospinal fluid tap test in patients investigated for idiopathic normal pressure hydrocephalus

SHORT STUDY TITLE / ACRONYM

Utility of 3D gait analysis in iNPH

PROTOCOL VERSION NUMBER AND DATE

version 2 - 08 September 2022

SPONSOR:

Northern Care Alliance NHS Foundation Trust

RESEARCH REFERENCE NUMBERS

IRAS Number:	302102
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FUNDERS Number:	Not applicable

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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 compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

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.

For and on behalf of the Study Sponsor:

Signature:
.....

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

Name (please print):
.....

Position:
.....

Chief Investigator:

Signature:
.....

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

Name: (please print):
.....

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STUDY SUMMARY

Study Title	Utility of 3-dimensional gait analysis in reference to clinical assessments to detect significant change after a cerebrospinal tap test in patients investigated for idiopathic normal pressure hydrocephalus
Internal ref. no. (or short title)	Utility of 3D gait analysis in iNPH
Study Design	Cross-sectional, controlled study
Study Participants	People with iNPH and healthy control participants
Planned Size of Sample (if applicable)	20 people with iNPH 20 healthy volunteers of similar age and sex distribution
Follow up duration (if applicable)	N/A
Planned Study Period	12 months
Research Question/Aim(s)	We aim to provide a detailed characterization of gait impairment in people with idiopathic normal pressure hydrocephalus (iNPH) to aid diagnosis and provide a platform for future work to objectively assess the effectiveness of treatment interventions using gait analysis variables as the main outcome measure. Our primary objective is to identify key gait and balance variables that can objectively characterize the mobility impairment in iNPH and that will also serve as measures to accurately quantify changes in mobility and balance before and after lumbar puncture to remove cerebrospinal fluid (CSF tap test or TT), a standard clinical procedure to assess whether patients may benefit from permanent treatment with a neurosurgical operation to drain CSF (shunt). Whilst the emphasis will be placed on objective laboratory-based measures, this work will also seek

	to validate robust clinical measures to support clinic-based assessments as potential surrogate measures and for instances where sophisticated gait analysis may not be accessible. We hypothesize that (i) those with iNPH will exhibit decreased gait velocity (slower walking), increased step width variability, unsteadiness (increased centre of mass trajectories), reduced joint ranges of motion, and poorer balance test scores, when compared to age-matched controls; (ii) gait outcome variables will improve following tap test; and (iii) gait analysis will be more sensitive than clinical assessments at demonstrating change, after CSF TT. We have experience identifying a selection of these variables as evidence of movement impairment from our extensive research with other clinical populations.

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
Hydrocephalus Association (HA) 4340 East West Highway, Suite 905 Bethesda, MD 20814-4447 301-202-3811 +888-598-3789 Fax: 301-202-3813 info@hydroassoc.org	2021 Innovator Award to the value of $ 50.000

ROLE OF STUDY SPONSOR AND FUNDER

Northern Care Alliance NHS Foundation Trust (NCA) is the sponsor of the study. The Hydrocephalus Association (HA), USA, is the funder of the study. The clinical research team is based at the NCA. The academic research teams are based at the Manchester Metropolitan University (MMU) and Gothenburg University (GU), Sweden. The clinical and academic research teams were solely responsible for the design of the study and manuscript writing and will be solely responsible for the data analysis and interpretation and dissemination of the results. The sponsor will ensure that the study conduct adheres to NHS standards.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

We have consulted a group of patients and carers living with iNPH for their views on the purpose of the study, and its accessibility, in terms of the potential burden of participating and the ease of understanding the participant information sheets. Their feedback was invaluable, and they expressed keen interest and gratitude for such a study given the significant impact the condition has on their quality of life.

PROTOCOL CONTRIBUTORS

The researchers of this study are the sole contributors to study design, data analysis and interpretation, manuscript writing and dissemination of results.

The sponsor's role and responsibility is to ensure that the study conduct adheres to NHS research standards. The funder's role and responsibility is to assess the study for scientific validity and funding.

KEY WORDS:	idiopathic normal pressure hydrocephalus, iNPH, gait analysis, outcome measure, CSF tap test

STUDY FLOW CHART

See appendix

STUDY PROTOCOL

Utility of 3-dimensional gait analysis in reference to clinical assessments to detect significant change after a cerebrospinal fluid tap test in patients investigated for idiopathic normal pressure hydrocephalus

1 BACKGROUND

Idiopathic normal pressure hydrocephalus (iNPH) is a progressive condition of gait, bladder and cognitive dysfunction(1). Results from prevalence studies indicate that around 2% of people aged 65 or above suffer from iNPH. Mean age is around 74 years, the majority of patients being in their 70ies and there is a slight male predominance (2). Demonstration of change in patients' mobility is crucial to inform diagnostic and therapeutic decisions at the stage of diagnosis and on follow-up after treatment (3). Current practice relies on manual mobility assessments such as the Tinetti gait and balance assessment tool, but changes can be difficult to detect, e.g., if gait is only mildly impaired or change is discrete. Furthermore, while video-recorded gait performance is often used before and after drainage of excess fluid during lumbar puncture (LP, "CSF taptest"), there is no universally accepted, standardised rating system (4). The test is therefore often rated as "improvement" or "no improvement". Literature reports of the CSF taptest vary in methodology and many reports are outdated. Few studies have used advanced gait analysis techniques for identification and monitoring of people with iNPH - of those that have, none has reported analyses - which include joint kinetics and kinematics, instead only reporting simple outcome measures that could be obtained through more rudimentary techniques (5-8). Therefore, there is a clear unmet need for a more sensitive gait analysis method to identify changes in mobility in people with iNPH . We believe this work will be the first to (i) provide a complete, detailed characterization of gait impairment in patients with iNPH compared to healthy controls using 3D gait analysis; (ii) identify and quantify changes after LP in gait in reference to standard clinical assessments; and (iii) explore thresholds to differentiate responders from non-responders to LP compared to standard clinical assessment methods with the aim of providing an objective reliable primary outcome variable for future randomised controlled clinical trials and to improve routine clinical care of patients. We therefore expect the outcomes of this work to inform future clinical care guidelines and further research into better diagnosis and treatment of people with iNPH.

2 RATIONALE

Currently, the comparison of suspected prevalence in epidemiological studies and the recorded number of treatments per year suggests that the condition is largely under-recognized in the world (9). This under-recognition of iNPH leads to continued suffering in many of those who are never diagnosed. We believe that the proposed project is both innovative and pioneering: in this first proof-of-concept study we aim to use advanced 3D gait analysis, which has not been used before in this context, to identify and quantify gait parameters typical for iNPH. Such methods could prove more sensitive at capturing changes when evaluating effects of CSF drainage procedures and at monitoring the efficacy of the permanent treatment, the surgical placement of a small plastic tube (shunt) draining fluid out of the fluid filled space in the brain (ventricle) into the abdomen (peritoneum), a VP shunt, than routine clinical assessments. It may also help to identify which individual or combination of clinical markers are most useful in the absence of 3D gait analysis. If they increased the sensitivity of the Tap Test to select candidates for shunt surgery, this would help avoid missing potential patients who should be offered treatment. Furthermore they could pick up early any deterioration in shunted patients or help document an improving trajectory after shunting.

In consultation with people with iNPH and their carers, both within the service and as part of a formal Patient & Public Involvement exercise, they have reported a significant toll of the condition on their quality of life. They were grateful that the condition was being studied and hoped to support any research which would improve understanding of iNPH. Studying a condition which affects the elderly is particularly important as many in this patient group feel forgotten about. In some cases, they feel as if their ailments are attributed to age-related changes, and hence are of less importance to healthcare providers. In conducting this research, we hope to improve awareness and understanding of the condition, and also the quality of lives of people with iNPH and their carers

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3 THEORETICAL FRAMEWORK

iNPH is a clinical syndrome consisting of prominent and progressive decline in mobility followed by less prominent but equally progressive decline in bladder function and cognition derived by analogy from NPH (1, 10) and distinguished from it by the absence of a preceding insult such as meningitis or subarachnoid haemorrhage, in the context of obligatory ventriculomegaly on brain imaging. The symptoms may improve by draining cerebrospinal fluid with a surgically inserted “shunt” (11). To evaluate the likelihood of shunt responsiveness people with iNPHs’ mobility is assessed before and after lumbar puncture draining a large volume of CSF (3), eg 50mls, mimicking the permanent procedure, for any indication of improvement. If improvement can be demonstrated probabilities of permanent improvement following CSF shunting is quoted at 80%. Demonstrating change, ie rating the tap test as positive or negative is challenging because there is no agreement on what assessments are best, how they should be used (4) and how to interpret the results if change is small because of a good baseline or discreet change. 3-dimensional gait analysis is a highly sophisticated laboratory technique providing objective quantitative measures of mobility combining the absence of operator dependence and high resolution enabling the demonstration of minute numeric change. It offers the opportunity to quantitatively characterise a neurological gait disorder (as opposed to the qualitative characterisation provided by the neurological examination, eg into “spastic”, “frontal” or “ataxic”) which has the advantage, again, of quantifying change (as opposed to the qualitative neurological examination which tends to remain unchanged albeit potentially “less severe”) and is in that respect similar to assessment scales such as the Tinetti gait and balance scale which calculates a score but its role in the tap test is not universally accepted. We will compare clinical mobility assessments with 3D in an attempt to validate a combination of clinical markers providing maximum discrimination between before and after.

4 RESEARCH QUESTION/AIM(S)

We aim to provide a detailed characterization of gait impairment in people with iNPH to provide a platform for future work to objectively assess the effectiveness of treatment interventions using gait analysis variables as the main outcome measure. We have experience identifying a selection of these variables as evidence of movement impairment from our extensive research with other clinical populations.

4.1 Objectives

Our primary objective is to identify key gait and balance variables that can objectively characterise the mobility impairment in iNPH and that will also serve as measures to accurately quantify changes in mobility and balance before and after lumbar puncture to remove cerebrospinal fluid (CSF tap test or TT), a standard clinical procedure to assess whether patients may benefit from permanent treatment with a shunt. Whilst the emphasis will be placed on objective laboratory-based measures, this work will also seek to validate robust clinical measures to support clinic-based assessments as potential surrogate measures and for instances where sophisticated gait analysis may not be accessible. We hypothesise that

(i) those with iNPH will exhibit decreased gait velocity (slower walking), increased step width variability, unsteadiness (increased centre of mass trajectories), reduced joint ranges of motion, and poorer balance test scores, when compared to age-matched controls;
(ii) gait outcome variables will improve following tap test; and
(iii) in view of the low negative predictive value but high specificity of the TT gait analysis will be more sensitive than clinical assessments at demonstrating change.

Secondary characterization objectives will aim to quantify general levels of everyday activity with a fitbit, psychological factors such as mood and levels of anxiety, quality of life and carer burden (the latter in patients only), and expectations and experience of gait analysis in healthy control participants and people with iNPH. We hypothesize that general levels of mobility (i.e. in everyday activity) will increase following TT; psychological factors (e.g. mood, expectations) may be considered as potential confounding, mediating and response variables.

4.2 Outcome

The primary outcome measures of the 3D gait analysis are the ‘dynamic balance’ that evaluates the movement (sway) in the body centre of mass relative to the centre of pressure under the feet, step length, gait velocity and temporo-spatial measures of gait variability.

The discriminant performance between groups and the screening characteristics for shunt surgery of gait analysis variables will be compared with those of the current standard clinical assessments. These include: 10m timed walk (number of steps and seconds), 360 degree timed turns (number of steps and seconds), Tinetti gait and balance assessment (score out of 28), timed up and go test (seconds), 6m walk test (minutes and seconds), single leg stand (seconds), Romberg test(seconds).

Secondary outcome measures quantify general levels of everyday activity with a fitbit, levels of anxiety and depression with the hospital anxiety and depression scale (HADS, score out of 21), quality of life with the EQ 5D 5L and carer burden with the Burden Scale for Family Caregivers questionnaire (patients only), and the experience of gait analysis in controls and people with iNPH before and after TT in a semi quantitative interview.

5 STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYIS

This pilot study will obtain data necessary to estimate the sample size for a large-scale, pivotal randomized controlled trial, including characterization of gait and balance data for patients with suspected iNPH. We will also obtain 1) estimate of variability of the follow-up and change scores on primary outcome measures; 2) correlation between baseline and follow up scores (r value); and 3) smallest clinically meaningful between-group effect for the primary outcomes.

We will use a 16-camera 3-dimensional motion analysis system to accurately track the movement of markers positioned on specific anatomical landmarks of each participant's body while walking. Force plates embedded in a bespoke floor-mounted walkway will provide accurate measurements of ground reaction forces under the feet as the participant walks across them. These measures will provide a detailed understanding of the movement of the limbs and whole body, and the rotational forces developed around all lower limb joints. We also have the ability to record muscle activity through surface electromyography, which provides insight into when, and by how much, muscles are being utilised to perform a task. We will examine gait with a range of support conditions (e.g. with natural use of preferred walking aid if required; with assistance from partner/carer/researcher; with use of a standardised minimal walking aid such as a cane/stick; and without any assistance if possible) to allow appropriate comparison against controls and pre-post treatment. Static balance will be examined through quiet stance (e.g. 30s standing on force plates; centre of pressure and centre of mass trajectories and their time derivatives to be analysed), and dynamic balance examined during gait. Continuous data sets will be generated and used to quantify different aspects of gait and balance function.

Gait variables of interest: The research team have extensive experience of investigating clinical movement impairment across a range of other clinical conditions including diabetes, stroke and Parkinson's disease. While measuring the full range of detailed gait variables, based on our experience and evidence from the literature, we hypothesise analysis may focus around some key variables. These include a measure of 'dynamic balance' that evaluates the movement (sway) in the body centre of mass relative to the centre of pressure under the feet, shown to be a sensitive measure of gait impairment in diabetic neuropathy (12). Other variables of focus based on previous research include step length, gait velocity and temporal-spatial measures of gait variability (13-15). Based on the team's clinical experience of iNPH gait and from our recent Patient and Public Involvement (PPI) sessions in preparation for this project, patients tell us they sometimes experience the feeling of their feet "sticking to the floor" and in this respect we hypothesise that the temporal-spatial gait variables (reflecting timing and distance of gait) events might be particularly pertinent.

Remote physical activity monitoring devices (Fitbits) will be supplied to all participants (patients and controls) when they attend for their first visit to the gait laboratory. Patients start monitoring their activity levels 7 days prior to their lumbar puncture until 7 days post-lumbar puncture; patients and controls will be asked to record the amount of daily activity during this time period. Controls will monitor their activity in the 7 days pre- and 7 days post-gait assessment. To mitigate any effects of the initial wearing of the monitor (i.e. gait-related changes), only the data from the final 3 days of the pre-LP (or gait assessment for controls) and 7 days post will be analysed.

Psychological factors will be monitored in patients (part of the clinical routine) and controls (when they attend the gait laboratory) using the Hospital Anxiety and Depression Scale. Quality of life will be assessed with the EQ-5D-5L patient version (patients -part of the clinical routine- and controls when they attend the gait laboratory) and EQ-5D-5L proxy versions (patients only, part of the clinical routine) and carer burden will be assessed with the Burden Scale for Family Caregivers (patients only, part of the clinical routine). These secondary assessments will provide insight into clinically-relevant outcomes of everyday activity in the period immediately following tap-test and may be relevant for the participants' performance. We will also evaluate participants' experience and expectations of their gait and balance performance pre and post tap test when measured clinically and with gait analysis, assessing for concordance and participants' reaction to the results using a questionnaire. Patients are followed closely after the TT as part of clinical routine to discuss the results and plan further management.

Key gait and balance variables that can be used to characterize iNPH will be determined through the use of logistic (discriminant) regression analyses between patients and healthy controls. Given the sample size of this

initial study, variables will be considered unifactorially. A similar approach will be used to estimate the Receiver Operating Characteristic (ROC) curve for these variables as screening tools for shunt surgery. Standardised effect sizes for the key gait and balance variables will be compared informally with those derived for currently routine clinical measures by repeating the above analyses.

6 STUDY SETTING

People with iNPH will be recruited from the regional specialist NPH clinic at The Manchester Centre for Clinical Neurosciences (MCCN) at Salford Royal Hospital, Northern Care Alliance, UK where they are assessed as part of their clinical routine by a senior neurologist with specialist interest in cognitive neurodegenerative disease, by a senior neuropsychologist with specialist interest in differential diagnostic assessments of patients with dementing disorders, advanced MRI scanning of the brain, lumbar puncture for cerebrospinal fluid neurodegeneration markers and clinical examination of gait and balance before and after TT carried out by a neurophysiotherapist prior to reaching a consensus diagnosis in the multidisciplinary team meeting (NPH MDT).

Healthy controls will be recruited in two ways. They may be spouses/carers of people with iNPH or they may be people from the general public who have responded to the study advertisement. We will aim to recruit the same number of controls as patients with a similar age and sex distribution but will not undertake individual matching.

Both groups will undergo the same laboratory-based testing protocols to assess their gait and balance in the gait laboratory at the MMU. Participants in the control group will be invited to attend a single testing visit at the gait laboratory. Participants with iNPH will be invited for a second test session the day after tap test to assess the effects of the procedure on gait (change score on outcome measures). Should the patient not feel well then this visit may have to be cancelled.

7 SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

Inclusion and exclusion criteria have been chosen purely on scientific grounds. Only patients able to consent and able to carry out all study assessments will be able to participate. All eligible patients attending the regional NPH clinic will be offered participation.

7.1.1 Inclusion criteria

Consenting males and females diagnosed with iNPH according to the international guidelines for diagnosing iNPH (16). Patients younger than age 60 may be included on a case by case basis.

Should be able to walk unaided for at least 20 steps at a time; walking aids will be permitted to reflect the reality of this condition for many patients.

Consenting healthy volunteers, of similar age and sex distribution, without iNPH. Chronic stable health conditions and chronic stable medications (e.g. hypertension on long term antihypertensive medication) with no substantive impact on performance and participation in this study as judged by the investigators are permitted.

7.1.2 Exclusion criteria

Excluded are participants with

Other confirmed medical or surgical conditions better explaining symptoms than iNPH (patients) or with substantive impact (eg Parkinson’s, osteoarthritis) as judged by the investigators (patients and control)

Secondary or obstructive hydrocephalus; previous surgical procedures for hydrocephalus (patients)

Amputation of lower limb/appendages

Musculoskeletal injury/recent lower-limb surgeries affecting gait or other musculoskeletal ailments affecting gait and balance performance as judged by the investigators.

Participants on specific medications (eg centrally acting) better explaining symptoms than iNPH (patients) or with substantive impact as judged by the investigators (patients and control)

Unable to carry out all study procedures.

Unable to comprehend informed consent.

7.2 Sampling

7.2.1 Size of sample

20 males and females with iNPH.

20 unmatched healthy volunteers of similar age and sex distribution.

We have determined the target sample size in anticipation that several gait variables will show complete discrimination between patients and controls and to develop preliminary estimates of variation (SD) in follow-up values and change scores following TT. We will also derive initial estimates of performance characteristics, such as area under ROC curve, for use of gait variables to screen for shunt surgery. Given the preliminary aims and multiplicity of candidate gait variables at this stage, all statistical significance values will be interpreted as indicative rather than definitive and no statistical power calculation would be appropriate

7.2.2 Sampling technique

All people with suspected iNPH referred to the MCCN at the NCA are assessed in the regional specialist iNPH clinic. The study will exclusively recruit people with iNPH from this clinic. Participation will be offered to all eligible people with iNPH.

Healthy volunteers can be relatives/friends/carers of people with iNPH but participation will also be offered by advert to members of the general public.

We will recruit until we have 20 controls and 20 patients before and after TT and retain those with partial data.

7.3 Recruitment

7.3.1 Sample identification

People with iNPH will all be recruited by the consultants/nurse of the regional specialist NPH clinic at The Manchester Centre for Clinical Neurosciences at Salford Royal Hospital, Northern Care Alliance, UK. They may either be localised from the waiting list for lumbar puncture or directly when seen in clinic.

Study participation will be offered to healthy volunteers who may be spouses/carers/friends of people with iNPH, to university staff, to people registered on join dementia research, to people studying at the university of the third age (U3A), via "shine", a UK charity dedicated to people with iNPH, social media (Twitter and any others) and other local retirement groups by advert.

Transport costs for 40 participants at £ 35 are available if required. A £25 inconvenience payment will be given to each participant.

7.3.2 Consent

Eligible people with iNPH will be explained the study and provided with a study participant information sheet by the consultant or nurse. The participants will have at least 24h to decide whether they wish to participate. They will have the opportunity to visit the gait laboratory before their first assessment and will be consented by a member of the study team prior to the first gait analysis assessment in written format. Adults unable to consent for themselves in accordance with the mental capacity act (2005) will be excluded from the study. Healthy volunteers will be consented in written format by a member of the study team.

8 ETHICAL AND REGULATORY CONSIDERATIONS

8.1 Assessment and management of risk

The risks of the study are assessed as small or non-existent. The tap test is part of the patients' routine medical care. In this study we are measuring participant's gait before and after this tap test with 3D gait analysis.

Two important practical issues for patients were highlighted during a patient group discussion: their reduced balance and mobility and risk of falls often requiring walking aids and their need to have quick access to a toilet. In order to ensure safe travel for patients to the research laboratory and back, transport will be facilitated. All facilities are easily accessible with wheelchairs. The safety of the patient in the laboratory will be ensured by providing a harness if required to avoid falls. Toilets are in easy reach from the laboratory. Inclusion and exclusion criteria are purely on scientific grounds and this includes that only patients able to consent will be able to participate. All eligible patients attending the regional NPH clinic will be offered participation. The only time when personal data will be passed from the medical research team to the academic research team is to enable the participants to attend the gait laboratory at the University. Confidentiality will be maintained at all times. There are standard procedures in place to ensure anonymisation and data safety.

The main burden for participants is that they give up their time for research, the need to physically access the gait laboratory requiring them to mobilise which is difficult due to their condition (iNPH) and their need to be able to access a toilet. Transport to the university will be arranged and easy access, including for wheelchairs, to the gait laboratory is ensured as is easy access to a toilet. Control participants should only suffer from permitted chronic stable health conditions without impact on study procedures/participation. All research is conducted in accordance with government guidance regarding Covid-19. Risk assessments are in place for all research activities and include managing Covid-19 risks. While there are some very minor risks to those participating in this study, including allergic reactions to tape and adhesives or becoming fatigued during the testing process, these are unlikely. We aim to minimise these risks as much as possible and will stop testing immediately if required. Plenty of opportunity will be provided for resting, and refreshments will be available. Any adverse event sustained by the participant during the study will be recorded in the case report form.

Participants or carers who disclose a risk to:

1. Themselves: such as suicidality, self-harm, self-neglect, or safety concerns in the home environment, will be referred to their relevant health and/or social care services e.g. General Practitioner, crisis or mental health team, community neurorehabilitation team, adult safeguarding team.
2. Others: such as neglect of care duties, aggression, coercion, controlling, or otherwise abusive behaviour, will be referred to their health and/or social care services e.g. General Practitioner, crisis or mental health team, community neurorehabilitation team, adult safeguarding team.

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

Before the start of the study, a favourable opinion will be sought from the UK Health Departments Research Ethics Service NHS REC for the study protocol, informed consent forms, patient and healthy volunteer information leaflets and advertisements.

- 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 Chief Investigator's responsibility to produce the annual reports as required.
- The Chief Investigator will notify the REC of the end of the study.
- 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 study is declared ended.
- If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.
- Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

Regulatory Review & Compliance

The study will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and other applicable guidance. Good Clinical Practice, Data Protection Act, GDPR and the Declaration of Helsinki

The study will not commence until all regulatory approvals are in place, which will include HRA Approval, REC Approval and confirmation from local R&D that the Trust has capacity and capability to carry out the research.

Amendments

None so far

8.3 Peer review

The study has received independent review by Andy Vail, professor of biostatistics at the University of Manchester.

The grant application panel at the Hydrocephalus Association (HA) performed an expert review prior to their decision to fund the study.

The scientific quality has been assessed between the research teams at Gothenburg University, Manchester Metropolitan University and the Manchester Centre for Clinical Neurosciences.

8.4 Patient & Public Involvement

The research team held two separate patient and public involvement events last year, one face-to-face at Manchester Metropolitan University and one online.

The aim of the study, the patient information leaflet and consent form and practical aspects were discussed.

Patients and carers emphasised the main difficulty being one of impaired walking and balance with risk of falls. Patients described their sensation of their feet “sticking to the floor”. Almost equally disturbing they described their need to frequently and urgently use the toilet.

With regards to the patients’ description of how they experience their difficulty walking, we hypothesise that the temporal-spatial gait variables (reflecting timing and distance of gait) events might be particularly pertinent.

Participants’ feedback showed that patients and carers appreciated the chance to contribute to the scientific understanding of the condition, in the hope that they would improve the lives of others also burdened by the condition.

In line with their two main symptoms (risk of falls and difficulty with bladder control) adaptations have been made in accordance with suggestions obtained during the events. This includes safe transportation, access for wheelchair users and toilets within easy reach.

Patients and carers also commented on the patient information leaflet and consent form. Their suggestions have been used to adapt them and make them comprehensible to non-specialists.

8.5 Protocol compliance

Accidental protocol deviations will be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol which are found to frequently recur will lead to immediate action and could potentially be classified as a serious breach.

Where necessary, a deviation from the protocol may lead to an amendment to the protocol.

8.6 Data protection and patient confidentiality

All investigators and study site staff comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act’s core principles.

Only the named members of the research team, and the MSc research student who will be appointed to collect data for this project, will have access to participants' personal data to enable participants attend the MMU gait laboratory. Apart from the research team, direct access will only be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections and the participants will have given written consent to that effect.

Medical records will only be accessed by the healthcare team.

All data used for analysis will be free of personal data, i.e. "pseudonymised" or "coded". Pseudonymisation takes place with the help of a code key generating numerical data stored in research databases that is stored in our study centres. The identification key is stored separately at our study centres. The identity of the study participants can be traced via a code key and is compiled as a consecutive numeric code. Only Richard Mills at MMU and Tobias Langheinrich at NCA have access to this code key. Dr Langheinrich acts as data custodian for this study.

The pseudonymised data will be analysed by researchers named on this application and will therefore be shared with or transferred to Salford Royal Hospital, Manchester Metropolitan University and Gothenburg University. Data will be shared only with password protected and encrypted methods.

All information and data collected during the course of this research will be kept confidential and will only be used for the purposes of this study. Electronic data from the study will be kept on password protected and encrypted university or NHS computers. Data from the questionnaires will be stored in locked filing cabinets. In both cases the data will be coded to protect participant identity. Only the Principal Investigators and other members of the research team will have access to the data, which will be stored for 10 years. After this time the electronic data will be deleted and the paper data will be shredded. The results of the study will be communicated at academic conferences or published in scientific journals. In this event, data will be presented in a manner that will not allow

participant identity to be determined. The data are generated as part of the participants' routine care and as part of their participation in the research arm of the study.

8.7 Indemnity

The study sponsor NCA is covered via the NHS indemnity scheme.

The collaborator MMU has insurance/indemnity arrangements in place.

8.8 Access to the final study dataset

All members of the research team have access to the full dataset.

The members of the research team will be consulted if any one member wishes to use the data for secondary analysis.

8.9 Monitoring and audit

The study will be subject to the standard procedures for monitoring and auditing of studies by the sponsor.

Any changes to the protocol will be agreed with the sponsor prior to submission to NHS research ethics committee for review with the exception of where urgent safety measures apply.

All staff working in the study will have completed appropriate training to undertake the duties delegated to them by the Principal investigator such an ICH-GCP.

9 DISSEMINIATION POLICY

9.1 Dissemination policy

Different types of research data will be obtained as part of this study. The data obtained as part of the patients' routine clinical care but forming part of the analysis of the study (history, examination, MRI brain, CSF results, clinical gait and balance assessments before and after lumbar puncture, neuropsychological assessment, HADS,) are owned by the NCA. The data from the 3D gait analysis, the fitbit,the HADS and the EQ-5D-5L (healthy volunteers only) will be owned by MMU. The HADS and EQ-5D-5L of the patients is part of their clinical record.
On completion of the study the data will be analysed and tabulated and a Final Study Report prepared.
The full study report will be held at the NCA and MMU.
The study is the joint effort of all investigators. All investigators have rights to publish study data.
Publication after the study has ended will occur within the ensuing year.
The funding body will be acknowledged in any publication.
Participants will be notified when the results have been published.
The dataset will be made publicly available on an open access repository at the MMU.

9.2 Authorship eligibility guidelines and any intended use of professional writers

All members of the research team will have authorship rights. Membership will be reviewed periodically by the existing members on the basis of the scientific contribution of potential new members. The research team does not act as part of a larger group or committee.

10 REFERENCES

List the literature and data that are relevant to the study, and that provide background for the study. Please ensure the text contains appropriate cross references to this list.

11. APPENDICIES

11.1 Appendix 1- Required documentation

CVs of the research team
Healthy volunteer information sheet
Patient information sheet
Consent form for patient
Consent form for healthy volunteer
Clinical research folder
Advert for patient
Advert for healthy volunteer

11.2 Appendix 2 – Schedule of Procedures (Example)

People with iNPH (research interventions only)

Procedures	**Visits (insert visit numbers as appropriate)**				
	Screening	**Baseline**	**Tap test**	**Day after tap test**	**after day 7 post tap test**
Informed consent	x				
Provision of fitbit	x				
Questionnaires pre TT (HADS, EQ-5D-5L patient and proxy versions, Burden Scale for Family Caregivers, expectations and experience of gait analysis, patient version)		x			
Gait analysis pre TT		x			
expectations and experience of gait analysis, patient version)				x	
Gait analysis post TT				x	
Collection of fitbit					x

Healthy volunteers

Procedures	**Visits (insert visit numbers as appropriate)**				
	Screening	**Baseline**	**After day 7 post gait analysis**	**Week 8**	**6 Months**
Informed consent	x				
Demographics	x				
Medical history	x				
Provision of fitbit	x				
HADS, EQ 5D-5L, expectations and experience of gait analysis questionnaire, control version	x				

Gait analysis		x			
Collection of fitbit			x		

13.3 Appendix 3 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

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SHORT TITLE/ACRONYM: Utility of 3D gait analysis in iNPH

13.4 Appendix 43 – Study flow chart

TIME POINT

PATIENT WITH INPH

ACTIVITY	ASSIGNED TO	LOCATION	TIME	END	0
PIL	doctor	HOSPITAL	0		
Visit to gait lab	researcher	GAIT LAB	AT LEAST 7 DAYS BEFORE TAP TEST		
Consent	researcher	GAIT LAB			
Tap test	doctor	HOSPITAL			
Visit to gait lab	researcher	GAIT LAB	DAY AFTER		

			TAP TEST																												

TIME POINT					**0**																										
HEALTHY CONTROL																															
ACTIVITY	**ASSIGNED TO**	**LOCATION**	**TIME**	**END**																											
PIL	Doctor or researcher	HOSPITAL/GAIT LAB	0																												
Visit gait lab (+/- consent +/- gait analysis)	Doctor or researcher	HOSPITAL	24H																												
Gait lab if not assessed during first visit (+ consent if not consented during prior visit)	researcher	GAIT LAB																													