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BRIEF REPORT

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Designing genetic studies for people with intellectual disabilities: Practical lessons from a pilot study

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Abstract

Genetic variations are overrepresented in people with intellectual disability (PwID), particularly those with physical and mental health co-morbidities, but remain significantly under-diagnosed. Lack of suitable research studies, a natural extension of the complexities posed of consenting and recruitment is considered culpable. There is a resultant dearth of evidence on establishing bespoke genetic studies for adult PwID. This report outlines the challenges faced in the implementation and administration of a pilot genetic study for adult PwID hoping to better inform future genetic study designs for PwID. Adult participants with a diagnosis of ID (ICD10 F70-F73) and epilepsy (ICD10 G40) were recruited to The **P**en**i**nsula study e**x**ploring genomic stratification in **i**ntell**e**ctual disability and epilepsy via the ethically approved Royal Devon and Exeter Tissue Bank (RDETB) (16/SC/016). Managed within the National Institute for Health Research (NIHR) Exeter Clinical Research Framework, the RDETB was set up to proactively collect and store 'spare' tissue from routine clinical procedures such as venepunctures for routine good practice biochemistry monitoring. Participants who satisfied the criteria for the need for routine bloods to monitor their general health were identified to be invited for participation. From October 2017 to March 2020 from a total caseload of 375 PwID and epilepsy, 291 were screened (77.6%), 116 (39.9%) identified as potentially eligible and sent study information and genetic samples obtained from 30 (8%). Analysis showed 75% of PwID had some biochemical abnormalities requiring further medical attention. The recruitment was influenced by the clinical care set up in implementing the sanctioned ethics. However, where bloods were achieved it proved to be beneficial in identifying hitherto undiagnosed medical problems. While the challenges to gain consent, are considerable, the reasonable adjustments needed to facilitate participation and the immediate clinical benefits where engagement was successful are significant.

KEYWORDS
genetics, intellectual disabilities, mental capacity, practice, research

INTRODUCTION

The Royal College of Psychiatrists (RCPsych, 2016) defines people with intellectual disability (PwID) as characterised by significant impairment of intellectual and adaptive functioning, with onset before the age of 18. Around 1%–2% of the UK population have an ID (Public Health England [PHE], 2016). PwID are more likely to have mental and physical health co-morbidity and premature mortality (Heslop et al., 2013; Shankar et al., 2020). Approximately 20% of PwID have recognised genetic impairments which predispose to physical, psychological and neurodevelopmental co-morbidities (De Villiers & Porteous, 2012; Palmer et al., 2014). Specific genetic disorders are associated with seizures, self-injurious behaviours and affective/psychotic illnesses (Kidd et al., 2014; Soni et al., 2008). The under-diagnosis of genetic disorders predisposes to symptom-based medication use, such as to manage challenging behaviour (Wolfe et al., 2017, 2018). Identifying genetic conditions linked to physical and mental disorders can reduce health inequalities and premature death, and aid PwID in understanding and managing their condition (Adlington et al., 2019). It can also be the pre-cursor for delivering personalised and precision treatments using vehicles such as pharmacogenomics (Perera et al., 2022). However genetic investigation is not routine practice for PwID and comorbid disorders in the United Kingdom (De Villiers & Porteous, 2012).

The **P**en**i**nsula study e**x**ploring genomic stratification in **i**ntell**e**ctual disability and epilepsy (PIXIE). This was a genetic research project (2017–2020), exploring the feasibility of identifying genetic variation in adult PwID with comorbid epilepsy. This feasibility prospective cohort study aimed to recruit adult PwID for genetic, epigenetic and transcriptomic analysis, to identify molecular markers that can be used to facilitate further studies or personalised medicine approaches to optimise treatment and care. Secondary aims included evaluation of recruitment rates, data collection methods and outcome measures, and assessment of the resources required for further genetic studies. The study was unique in being designed specifically for PwID by ethically combining research ambitions of genetic sampling with improving clinical practice. Eligible participants were overdue clinically-indicated biochemistry, ensuring meeting a major clinical need. This paper presents the strengths and weaknesses of PIXIE to provide learning for future study designs. PIXIE genetic results are to be reported separately.

METHODS

Participants with a diagnosis of ID (ICD10 F70-F73) and epilepsy (ICD10 G40; World Health Organisation [WHO], 1993) over the age of 18 years, that is, adults, were identified by clinicians working in the adult ID neuropsychiatry service at the Cornwall Partnership NHS Trust Sites (pop: 538000) and recruited to PIXIE via the ethically approved Royal Devon and Exeter Tissue Bank (RDETB; 16/SC/016). Managed within the National Institute for Health Research (NIHR) Exeter Clinical Research Framework, the RDETB was set up to proactively collect and store 'spare' tissue from routine clinical procedures such as venepunctures for routine good practice biochemistry monitoring. PIXIE study methodology, consent issues and processes are provided In Supplementary Information S1. Consent was witnessed and formally recorded.

TABLE 1 Demographics and clinical data for participants with ID

Age	Mean = 45.5 years SD = 19.6
Sex	Male = 19 (63.3%) Female = 11 (36.7%)
ID type	Mild = 9 (30%) Moderate = 8 (26.7%) Severe = 13 (43.3%)
Number of psychotropic drugs	Mean = 0.79 Range = 5
Number of Anti-Seizure medication	Mean = 1.87 Range = 4
Number of other drugs	Mean = 1.4 Range = 6
Number of diagnoses	Mean = 3.5 Range = 4

Abbreviation: ID, intellectual disability.

TABLE 2 Breakdown of recruitment of PwID for PIXIE study

Total active epilepsy caseload of countywide learning disability team	375
Screened for eligibility for Pixie study	291 (77.6% of total caseload)
Identified as potentially eligible and sent study information	116 (39.9% of those screened)
Research clinic appointments made	56 (48.3% of those eligible)
Consented and research blood samples obtained	30 (53.6% of those booked)
Consented but no research bloods obtained	9 (16.1% of those booked)
Non-attendance[a]	16 (28.6% of those booked)
Participants with capacity to consent	5 (16.7%)
Participants for whom proxy consent was provided by a Consultee	25 (83.3%)

Abbreviations: PIXIE, **P**en**i**nsula study e**x**ploring genomic stratification in **i**ntell**e**ctual disability and epilepsy; PwID, people with intellectual disability.
[a]Most common reasons cited for non-attendance were unpredictable changes in the mood, behaviour and/or physical health of PwID, changes in their social circumstances, unavailability of support staff and transport difficulties.

TABLE 3 Recommendations for design and resourcing of genetic studies for people with ID

Recruitment, mental capacity and gatekeeping

- Facilitate access for staff at group homes for PwID to training on the necessity and recommended frequency of clinically indicated blood monitoring, supported by provision of patient/carer held record
- Increase awareness staff at group homes for PwID of funded training modules by organisations such as NIHR on good practice research in PwID
- Further research is indicated to clarify best practice for recruitment of people with ID who lack capacity to consent to research participation where no Next of Kin is identified
- Consider resourcing for provision of an independent advocate such as an IMCA to support Best Interests decision-making over research participation in the absence of a Next of Kin
- Develop an integrated clinical research pathway for PwID between all stakeholder organisations, including liaison psychiatry and primary care
- Develop a checklist of key considerations for research-related reasonable adjustments.
- Better training in genetics is needed for clinicians working with PwID, particularly on the diagnostic value it provides
- Integrate genetic testing more closely within a diagnostic pathway to increase the proportion of consultees that view the participation of PwID as of clear benefit to them and in their best interests

Reasonable adjustments

- Consider saliva kits as an alternative to obtaining blood samples
- Establish formal agreements to collaborate with learning disability liaison services in making accessible to PwID opportunities to participate in genetic research, such as facilitating genetic testing under general anaesthetic during routine care
- Explore prescribing access to local anaesthetic cream

Abbreviations: ID, intellectual disability; IMCA, Independent Mental Capacity Advocate; NIHR, National Institute for Health Research; PwID, people with intellectual disability.

RESULTS

Recruitment

From October 2017 to March /2020 from a total caseload of 375 PwID and epilepsy, of whom 291 were screened (77.6%). Of these 175 (60.1%) had suitable and up to date biochemistry thus were excluded. Thus, 116 (39.9%) were identified as potentially eligible and sent study information and genetic samples obtained from 30 (8%). Five participants provided informed consent while 25 could not and the assent processes established using the principles of the Mental Capacity Act were used. Demographics and extracted clinical data are detailed in Table 1, and detailed recruitment breakdown is in Table 2. The pandemic (March 2020) led to recruitment closure due to restriction of non-essential face-to-face contact.

The mean interval between clinical biochemistry obtained for PIXIE and previous biochemistry was 385 days, with a range of 1726 days. In total, 13 individuals had lacked biochemistry for over a year prior PIXIE.

Biochemistry findings

Results were unavailable for two participants. Analysis showed 75% of PwID had some biochemical abnormalities requiring further medical attention. Major ones included 32.1% of PwID having abnormal Thyroid-Stimulating Hormone levels and 28.6% cholesterol and/or triglyceride abnormalities. Abnormal prolactin levels were revealed in 45.5% of 11 participants where it had been requested.

DISCUSSION

PwID are excluded from most research, particularly interventional such as genetics and drug trials, as they can be

challenging to consent and can find invasive procedures distressing. However, given the complexity, heterogeneity, co-morbidities and health vulnerabilities they remain the group most in need of bespoke research insights. This project has succeeded as a feasibility study for reasons outlined in Appendix A.

PIXIE recommendations on study design for genetic studies of PwID are outlined in Table 3, and key areas are discussed here.

Recruitment, mental capacity and gatekeeping

The challenges to recruitment of PwID to genetic studies relating to informed consent are well documented in literature (Adlington et al., 2019; De Villiers & Porteous, 2012). The International Association for the Scientific Study of Intellectual Disabilities advice in the absence of family members, collective professional decision-making is the most effective way to safeguard the potential research participant's best interests (Dalton & McVilly, 2006). For PIXIE it had been designed for family/friend to give proxy consent/assent as 83% of potential participants lacked capacity. Although research participation was paired with clinically indicated blood monitoring, many residential home staff declined to facilitate a Best Interests model of substitute decision-making in the absence of an Independent Mental Capacity Advocate (IMCA). Unwillingness or inability of support workers to facilitate participation of PwID in research involving invasive procedures is common and our study confirms it (McAllister et al., 2013).

Reasonable adjustments

PIXIE participation was facilitated by reasonable adjustments, to maximise uptake of blood tests (PHE, 2017). These included Easy Read information and allowing longer appointment durations than typically available through primary care phlebotomy. PIXIE recruitment challenges reflected the literature on some PwID being reluctant to participate in invasive tests, and reporting needle-related anxiety (Clough et al., 2016).

For PwID likely to experience extreme distress undergoing venepuncture, current practice is of taking samples during sedation for medically indicated procedures (dental check/scans etc.) (De Villiers & Porteous, 2012). This pathway was identified for enabling bloods in 15 PwID whose families had assented. Proactive attempts were made to utilise liaison pathways with the general hospital but were successful with only one participant. Frequent short-notice appointment changes and the lack of a research champion within the liaison pathway were significant factors. Prescribing issues, that is, unavailability of local anaesthetic cream requested by a further four potential participants prevented their recruitment. Another alternative could be the use of saliva as a method of genetic sampling. It is noteworthy that the genetic extraction yield is significantly greater from blood than saliva samples (Hu et al., 2012). Enabling saliva samples too would require a degree of co-operation from the participant.

Protocol barriers to recruitment

Tissue Bank Ethical Approval specified that research bloods were to be taken only at the time of routine clinical procedures. PIXIE eligibility criteria were also informed by various national guidelines for epilepsy or psychotropic drug monitoring recommending a maximum interval of 6 months for regular monitoring of side effects (National Institute for Clinical Excellence [NICE], 2018, 2020; RCPsych, 2016). In the sample screened for eligibility this standard had already been achieved in primary care for 60.1% of PwID, thereby excluding them from PIXIE eligibility. Thought could have been given to encapsulate PIXIE across care settings including primary care.

This was an exploratory pilot study and did not involve giving feedback to individual participants. This can present a barrier as clinicians could struggle to identify potential benefits to communicate to patients and carers to enable recruitment. There is need for clinician training in this matter (Adlington et al., 2019; De Villiers & Porteous, 2012). Research evidence following genetic testing and its feedback on participant quality of life outcomes is sparse and if improved, may influence referral rates from healthcare teams (Adlington et al., 2019). It is worth highlighting that this study findings are derived from those likely hardest to recruit and conduct blood tests on. However, the principles established would apply to most or all of this vulnerable community.

Biochemistry clinical findings

The study primarily aimed to recruit PwID who presented with significant barriers to routine venepuncture. Given the evidence of poorer health outcomes, and the potential of iatrogenic harm from psychotropic and anti-seizure medication the findings of clinically relevant abnormal biochemistry in 75% of participants were significant highlighting that there is continued value in the

study design to assimilate clinical and research work for this vulnerable group.

Co-production

An important element missed in the study is "bottom-up" co-production involving PwID and their families. Finding a representative expert population to meaningfully contribute to such complex and heterogenous studies can be challenging. However, given the importance of the topic and its future relevance and expected expansion there needs to be increased discussion on how to make such projects inclusive to capture views and opinions of experts by experience (Alexander et al., 2021; Perera et al., 2022).

CONCLUSION

PwID require being integral to the research process both as experts by experience and participants (Alexander et al., 2021). There are rewarding successes and a lot to still 'get right' as this report demonstrates. It is important for the research community to learn and share about challenges to gain confidence in researching such vulnerable cohorts.

AUTHOR CONTRIBUTIONS

All authors satisfy the ICMJE guidance by substantially contributing to the design, analysis and interpretation of the work, drafting of the manuscript, final approval of the article and all agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work is appropriately investigated and resolved.

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CONFLICT OF INTEREST

Rohit Shankar has received institutional and research support from LivaNova, UCB, Eisai, Veriton Pharma, Bial, Averelle and GW pharma outside the submitted work. No other author has any declared conflict of interest related to this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients under the PIXIE study were approved by the Royal Devon and Exeter Tissue Bank (RDETB) Steering Committee in 2017 compliant with their Ethical approval in August 2016 from the South Central - Oxford C Research Ethics Committee number 16/SC/0162 (a 5-year extension following initial approval 11/SW/0018).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A

Peninsula study e**x**ploring genomic stratification in **i**ntell**e**ctual disability and epilepsy Feasibility Study achievements

- identified clinical infrastructure failures
- led to important findings for individual participant's clinical care
- led to improvements in the clinical service
- identified the potential of combining research sampling with routine sampling
- Identified what would be needed to optimise recruitment in terms of specialist services, ranging from the simple (Emla cream) through to improving liaison pathways
- established a small biobank for preliminary epigenetic research