Reference Number II-LB-0315-20006

National Institute for Health Research

National Institute for Health Research (NIHR)
Invention for Innovation

Final Report Form

IMPORTANT

All projects funded through the Invention for Innovation programme are required to submit a report at the end of the funding period in order to:

- Ensure accountability
- Provide quality assurance
- Aid in appropriate dissemination of project results
- Understand the anticipated impact of the research
- Demonstrate the achievements of the research

The report must be a concise, standalone summary of the research; hence including large amounts of copied material should be avoided.

You will also be required to submit a final statement of expenditure at the same time as your report.

Information contained in this report and any related document(s) is of great value as it allows us to review and assess the outcome and outputs of the research we fund. This enables us to ensure that research has been carried out in accordance with our programme objectives and is vital for future planning and strategy setting.

Unless otherwise agreed, a draft report must be provided within two weeks of the project end date. Failure to submit may cause the final payment to be delayed.

The NIHR is committed to making the findings of the research that it funds publicly available. This report or sections thereof, in particular the scientific and plain English summaries, may be published, considering confidential and commercially sensitive information.

For office use only

Region

Date submitted

1. Project Details

Project Title: Evaluation and validation of a breath ammonia measurement technology for the improved management of patients with urea cycle defects.

Reference Number: II-LB-0315-20006

Contracting Organisation: University Hospitals Bristol NHS Foundation Trust

Approved Duration: 24 months | Current Duration: 36 months

Extension: 12 months

Start Date: 14 November 2016

End Date: 31 October 2019

Original Award: £713,623.00 | Current Award: £713,623.00

2. Chief Investigator

Title: Prof

Surname: Hamilton-Shield | Forename: Julian

Role in Project: Chief Investigator

Organisation: University of Bristol

Email Address: J.P.H.Shield@bristol.ac.uk

3. Research Team

Joint Chief Investigator		
Title: Professor	Surname: Killard	Forename: Tony
Organisation: BreathDX (UK) Limited		
Role in project: Chief Technological Officer, BreathDX (UK) Limited		
Co-investigator 1		
Title: Dr	Surname: Chakrapani	Forename: Anupam
Organisation: Great Ormond Street Hospital for Children NHS Foundation Trust		
Role in project: Consultant in Paediatric Metabolic Medicine		
Co-investigator 2		

Title: Dr	Surname: Champion	Forename: Mike
Organisation: Evelina London Children's Hospital, St Thomas' Hospital		
Role in project: Consultant in paediatric inherited metabolic diseases and clinical lead		
Co-investigator 3		
Title: Dr	Surname: Vijay	Forename: Suresh
Organisation: Birmingham Children's Hospital NHS Foundation Trust		
Role in project: Consultant in Inherited Metabolic Disorders		
Co-investigator 4		
Title: Dr	Surname: Joanne	Forename: White
Organisation: University of the West of England		
Role in project: Qualitative research and PPI Lead		
Co-investigator 5		
Title: Dr	Surname: Marques	Forename: Elsa
Organisation: University of Bristol		
Role in project: Health Economist Lead		
Co-investigator 6		
Title: Dr	Surname: Pierre	Forename: Germaine
Organisation: Bristol Royal Hospital for Children		
Role in project: Consultant in Paediatric Metabolic Disease		
Co-investigator 7		
Title:	Surname:	Forename:
Organisation:		
Role in project:		
Co-investigator 8		
Title:	Surname:	Forename:
Organisation:		
Role in project:		
Co-investigator 9		

Title:	Surname:	Forename:
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Role in project:		
Co-investigator 10		
Title:	Surname:	Forename:
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Role in project:		
Co-investigator 11		
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Role in project:		
Co-investigator 12		
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Role in project:		
Co-investigator 13		
Title:	Surname:	Forename:
Organisation:		
Role in project:		
Co-investigator 14		
Title:	Surname:	Forename:
Organisation:		
Role in project:		
Co-investigator 15		
Title:	Surname:	Forename:
Organisation:		
Role in project:		

4. Involvement of NIHR Infrastructure

Please indicate which NIHR Infrastructure organisations were involved in your research.

☐	HTCs	☐	INVOLVE	☐	NOCRI
x	BRC/BRUs	☐	DECs	☐	CTUs
☐	CRFs	x	CRN	☐	Other

Please describe the role of each organisation in your research. (***500 words***)

The original concept was developed, and exploratory Patient and Public Involvement (PPI) was conducted in the Bristol BRU Nutrition. In Bristol BRC (Nutrition Theme), qualitative research staff (RA: Georgia Herbert) developed the original themes for family interviews and then analysed data collected with Dr Jo White. Database management and electronic data capture was devised and collected by the Nutrition Theme's database manager (Stu Toms). Office space for the project manager (Fiona Lithander) was provided within the Nutrition theme's offices. The CRN assisted with site and patient recruitment.

5.Changes to Research Team

Please outline any changes that have been made to the research team over the course of the research, including an explanation of why they were required (***750 words***).

Dr Fiona Lithander was added to the team as AmBeR Research Manager in 01 April 2017.

Dr Anupam Chakrapani replaced Dr Lara Abulhoul at Great Ormond Street Hospital as a co-applicant mid-2017. Dr Chakrapani is a Consultant in Paediatric Metabolic Medicine.

Prof Richard Luxton replaced Prof David Evans as University of West of England (UWE) Lead mid 2017. Dr Jo White replaced Prof David Evans as the PPI Lead and Head of Work Package 2. Dr White is a Senior Research Fellow at UWE and is a member of the project Management Group.

Dr Germaine Pierre replaced Prof Julian Hamilton-Shield as Principal Investigator at University Hospitals Bristol early 2018, and Prof Julian Hamilton-Shield remains Chief Investigator on the Study.

Dr Termeh Admadraji, Project Manager at BreathDx left the study team early 2019 to take a position elsewhere.

6. Scientific Summary

Please provide a structured summary of your work, covering the following points concisely:

- Background
- Original objective(s)
- Methods (including patient and public involvement and, if applicable, study registration number, e.g., ISCRTN and/or PROSPERO)
- Key findings
- Outputs, impact and dissemination
- Conclusions
- Future plans

This summary may be made publicly available, therefore please do not include any information that is confidential or commercially sensitive at the time of submission. If you are in any doubt, please contact your NIHR programme team (***500 words***).

Background and objectives: Urea Cycle Defects (UCDs) are a group of rare congenital metabolic diseases relating to the enzyme pathways involved in the detoxification of nitrogen. The inability to effectively eliminate nitrogen leads to the build-up of several intermediates, including ammonia, which

is neurotoxic and causes hyperammonaemic encephalopathy.

The aim of this project was to establish whether the AmBeR device, a breath ammonia, home measurement prototype, could be used to improve the management of patients with UCD, potentially allowing them to self-monitor breath ammonia at home, avoiding unnecessary hospital visits and improving quality of life.

Methods: There were two parts to the AmBeR project:

Clinic Study, cases (children and young adults with a UCD or another hyperammonaemic (HA) condition) and controls (children and young adults with another inherited error of metabolism (IEM) without HA) were recruited from metabolic disease clinics of four UK tertiary hospitals. Data were collected on blood and breath ammonia, health related quality of life (HRQoL) and dietary intake.

Home Study, patients with a UCD or another HA condition were asked to collect breath ammonia twice daily at home for three months. Other data collected were patient and primary carer HRQoL, healthcare resource use, diet and hyperammonaemia symptomology. PedsQL scores were mapped to health utilities in the EQ-5D questionnaire. Twelve qualitative interviews were carried out to capture family experiences of living with UCDs. The study was registered with ISCRTN, number 98291277. PPI involvement included regular communication with 19 families and family membership of the study Steering Group.

Key findings:

1. There was good operability of the instruments in both the clinical and home environments. Qualitatively, the sensors do respond to breath ammonia in a predictable manner (breath ammonia is detectable and produces a qualitatively robust response) but not in a sufficiently reliable quantitative manner. The manufacture of the device sensors currently is not reliable enough to ensure they all responded equally.
2. Parents and carers are very keen on the conceptual idea to improve the day-to-day care of their children. Use of the device in general was patient/family acceptable.
3. The quality of life of children and young adults with UCDs and other HA conditions is poor when compared with other children with IEMs

Outputs, impact and dissemination: Clinic Study results have been presented at international conferences and discussed with families at Metabolic Support UK meetings.
Conclusions: Patients were able to use the AmBeR device to try and monitor breath ammonia levels in the clinic and at home. Whilst the device was usable by children, significant further work is required to improve the reliability of the sensors before the system can be considered for deployment clinically.
Future plans: Immediate activity by BreathDx will focus on the final technical development of the AmBeR breath measurement systems. These systems will be tested on a patient cohort with higher levels of breath ammonia, such as liver disease patients. Once validated, the technology will be used for a large-scale RCT covering all major metabolic centres in England and Wales.

Keywords (up to eight):

Provide up to eight key words in alphabetical order, which accurately identify the report's purpose, method and focus. Please use the Medical Subject Headings (MeSH®) thesaurus headings where possible.

https://www.nlm.nih.gov/mesh/MeSHonDemand.html

1. Ammonia
2. Child
3. Family
4. Hyperammonaemia
5. Metabolic diseases
6. Quality of Life
7. Young adult
8. Urea cycle disorder

7. Plain English Summary

Please provide a plain English summary of your research including where appropriate:

- Aims and objectives
- Background
- Methods
- Key findings
- Dissemination, outputs and impact
- Patient and public involvement
- Conclusions and future plans

A good quality plain English summary providing an easy to read overview of your whole research will help:

a) inform others about your research findings such as members of the public, health professionals, policy makers and the media
b) the research funders to publicise the findings.

It is helpful to involve patients / carers / members of the public in developing a plain English summary.

The plain English summary is not the same as the scientific abstract - please do not cut and paste this or other sections of your application form to create the plain English summary.

Useful links:

INVOLVE http://www.invo.org.uk/resource-centre/plain-english-summaries/

Access to Understanding: http://www.access2understanding.org/guidance/

The Plain English Campaign guide on medical writing: http://www.plainenglish.co.uk/free-guides.html

(***300 words***)

Background: Urea Cycle Defects (UCDs) are rare genetic disorders mostly affecting children. Protein eaten or coming from our muscles contains nitrogen, which can be poisonous if not removed from the body. However, children with UCDs are not able to process the nitrogen and it builds up as ammonia inside the body. High ammonia levels can cause learning difficulties or can lead to coma and death. Currently, doctors tell if a child is sick by testing ammonia in their blood, which is difficult to do well and needs a hospital attendance.
The aim of this study was to develop a machine that could measure ammonia in the breath. It is believed that the ammonia in breath is related to ammonia in the blood. This machine would allow people with UCDs to monitor their own ammonia levels at home without having to go to the hospital for ammonia blood tests.
Methods: Patients with and without UCDs were asked to take part. During clinic they provided a breath sample which we matched to their routine blood ammonia sample. They also completed some questionnaires. Some families volunteered to take the machine home for 3 months to collect breath samples and complete diaries about how the family and patient felt.
Key findings: The machine works well and is relatively easy to use. We need to improve 'the sensor' reliability. Families are keen to improve the daily quality of life of children with UCDs as it is significantly less than other children.
Dissemination, outputs and impact Results presented at conferences in USA/Europe and yearly at Metabolic Support UK meetings.
Patient and public involvement Families have engaged from the start and actively provided valuable feedback on study design, dissemination and their hopes for the future.
Conclusions/future plans Further work is needed to improve machine reliability before routine use.

Y	Please tick the box if this section of the report has been written with members of the public who have been involved in the research.

8. Aims and Objectives

Please describe the original aims and objectives of the research (***250 words***).

The aim of this research is to establish whether the AmBeR system can be used to improve the management of patients with UCD through the following objectives:

1. Establish that the developed device can be used effectively to measure ammonia in the breath of UCD patients

2. Establish that the device can be used to predict blood ammonia accurately and reproducibly across the clinically relevant concentration range in UCD patients

3. Demonstrate that the device can be used effectively in the home for self-testing

4. Demonstrate that use of the device could facilitate remote (from the clinic) decision making and disease management

5. Estimate the costs of hospital admissions and parental burden for children with UCD.

6. Estimate the quality of life for parents and children living with UCD.

9. Changes to Aims and Objectives

If the aims and objectives changed, please explain in what way and why (***250 words***).

They have not changed.

10. Description of Research

Please provide a structured summary of your work using the subsections below.

Background Urea Cycle Defects (UCDs) are a group of rare congenital metabolic diseases relating to the enzyme pathways involved in the detoxification of nitrogen via the urea cycle. The inability to effectively eliminate nitrogen can lead to the build-up of several intermediates, including ammonia, which is neurotoxic and causes hyperammonaemic encephalopathy (HE). UCDs are estimated to occur in 1:8,500 live births. There are an estimated 600 sufferers nationally with global estimates of 250,000, although it is probably under-reported. These rare mutations typically go unidentified at birth until such time as the patient presents with an HE event, usually due to an intercurrent illness. These encephalopathic events are difficult to manage, often requiring haemofiltration/dialysis and intensive care management. Coma and death are regular sequelae, as is significant neurological damage, leaving sufferers and their families with the lifelong management of neurological and cognitive disability, as well as the UCD itself. The effects of HE can range from no visible symptoms, loss of appetite, vomiting, lethargy, mild confusion, sleep disruption, delusions, hallucinations, and coma and, in extreme cases death. Currently, diagnosis is based on neurological assessment and measurement of blood ammonia and amino acid levels. Measurement of systemic ammonia is an objective and quantifiable measure of the extent of HE. The accurate sampling of blood for ammonia is technically challenging and self-testing of blood ammonia is not diagnostically viable. The correlation between blood ammonia levels and visible symptoms is poor. Chronic management of UCD is principally by way of dietary control of protein plus regular carbohydrate intake. However, dietary management may not be sufficiently optimised for individual patients for a given time, contributing to developmental impairment. Acute episodes arise due to intercurrent illness, predominantly infections, which disrupt normal dietary management, and which can trigger an elevation in systemic ammonia levels. Acute episodes can be treated with ammonia scavenging drugs and haemodialysis in the most extreme circumstances. However, as accurate determination of the status of the patient from visual symptoms

is unreliable, management is typified by a high index of suspicion on the part of carers, which must then be confirmed by the specialist care centre. This care strategy results in considerable disruption to the life of families, as well as the unnecessary repeated accessing of specialist care centres. This also imposes potentially avoidable costs on patients, carers and the NHS. There is also little longitudinal information on the impact of systemic ammonia levels in UCD patients. It is not known whether ammonia levels remain chronically elevated between acute episodes, or whether such chronic elevation leads to further developmental impairment. AmBeR is a prototype device developed by Breath Dx for monitoring breath ammonia levels. It is designed to allow patients to self-monitor their ammonia levels at home, avoiding unnecessary hospital visits thus improving the quality of life of the children with UCD and their parents. In the future, AmBeR may be adapted for further home self-management in other conditions and patient groups.

Methods Whilst there were eight work packages for brevity, this section describes six important methodologies:

(1) PPI Involvement: with assistance from the family-based charity, CLIMB (Metabolic Support UK) we held two PPI events (one in Bristol:4 families with UCDs) at the CLIMB national meeting (seven families) in October 2017 after HRA approval in August. A PPI Advisory Group (PPIAG) was also developed to increase family access to our study design. Members of the PPIAG attended two of the steering group meetings advising in all aspects of study development from device manufacture to family information sheets.

(2) Device and sensor refinement: With input from (1) and (3) devices for the home study (4) were manufactured for Breath Dx by Gentian. Sensor variability identified in (3) was subject to additional laboratory investigation by Breath Dx.
Figure: Device used in home study

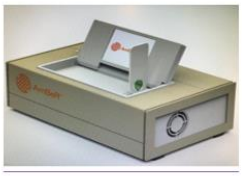


Figure 1: AmBeR UCD device

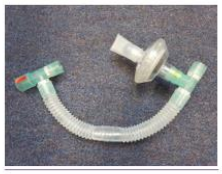


Figure 2: Breath sampling tube

(3) Hospital clinic study: In four participating centres (GOSH, Guy's/St Thomas's, Birmingham and Bristol Children's Hospitals) patients were recruited at routine clinic appointments. After re-adjustment from Birmingham, we planned to recruit forty-eight young people with hyperammonaemic conditions (HA) and a similar number of controls with IEMs but no issues with hyperammonaemia. After receiving nurse training on the AmBeR device and having had a routine blood test for blood ammonia levels, the young people then breathed into the AmBeR device eight times and the breath ammonia data recorded in the machine. Blood and breath ammonia were linked by an anonymised study number for later analysis. Contemporaneously, parents and young people completed a quality of life assessment using the validated PedsQ4 and a summary of their current state of wellness.

(4) Home testing of breath device in UCD families: Subsequent upon study 3, families were approached from within the UCD group for recruitment to the home study in which detailed daily diaries about health were recorded, an economic questionnaire was filled in by parents concerning personal expenses and use of NHS (hospital and GP appointments, attendance at A&E etc). Each day, patients were asked to breath into the device twice a day recording dates on the device to later correlate with their clinical symptom diary.

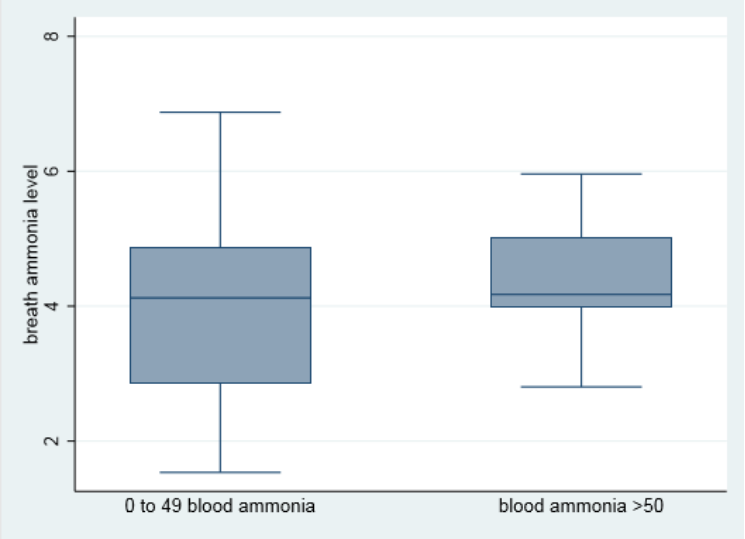
(5) Quality of life and economic utilities: We mapped PedsQL scores to EQ-5D utility weights for the UK population, using Khan et al's recommended mapping algorithms (models 5 and 6) (Khan KA, et al. Mapping EQ-5D utility scores from the PedsQL generic core scales. Pharmacoeconomics 2014;32(7):693-706). EQ-5D utility values are anchored at zero (for death) and range from negative values (health state worse than death) to 1 (best imaginable health).

(6) Qualitative research on the 'lived experience' of twelve patients and families with UCDs (parents of 13 children and young people ages eight to 21 years of age). One interview was conducted with an 18-year-old living with a UCD independently. These were collated by telephone interview using a thematic question set with time for participant free flow comments. The data was analysed using the framework method by two experienced qualitative researchers.

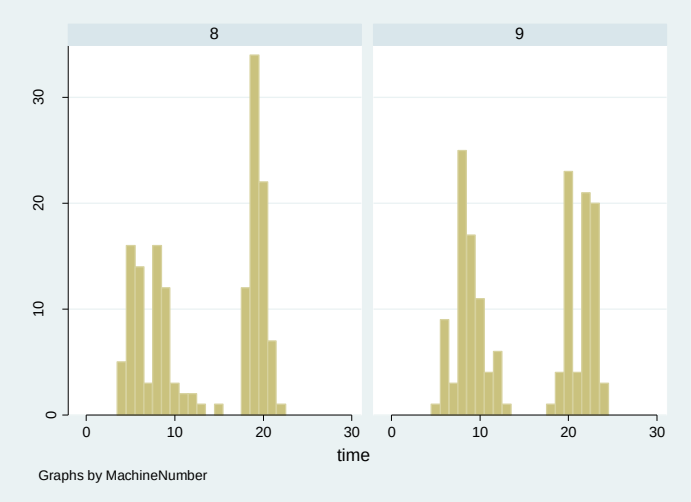
Findings

(i) **Recruitment**: In the clinic study (3), recruitment was excellent with 100% recruitment of Hyperammonaemia patients (n=48) and 96% of controls (n=46). Eighteen patients (90%) were recruited and provided written consent and/or assent to the home study (4). One family later withdrew leaving 17 (85%) completing study. Twelve interviews have been completed with families living with a Urea Cycle Defect.

(ii) **Finding of hospital-based, clinic study 3**: The range of ammonia levels when visiting clinic for UCD patients was from 9 to 170µmol/L, only 3 were above 100µmol/L (9%) and 65% (21/32) were less than 50µmol/L (~upper range of ammonia levels in non-HA population). All clinical and sensor response data were gathered, cross-checked and collated. A total of 51 valid data points with both breath and blood ammonia data were obtained. All breath ammonia data was qualitatively analysed and categorised as either test failures, suspect results or negative responses. Data was analysed using the relative impedance (Zf/Z0-1), and the change in impedance (Zf-Z0). No correlation was seen with the relative impedance. However, correlation was seen with the change in impedance (Pearson r=0.78), although there were some notable outliers, which were excluded. The graph below demonstrates breath ammonia levels (arbitrary units) in those having a normal blood ammonia (≤50 nmol/l) Column 1, compared to breath ammonia in those with high blood ammonia levels (>50 nmol/l) Column 2.

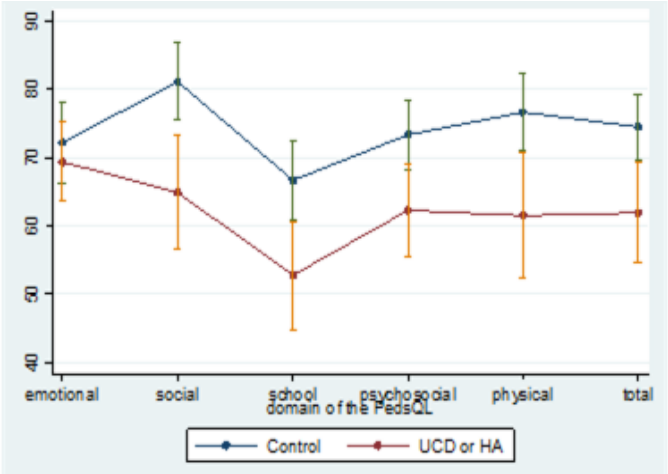


(iii) **Home data:** 18 families were recruited to the home study and 17 provided data. Impedance responses from sensors following breath sampling on a twice daily basis was performed for periods of approximately 3 months, which is in the final stages of data processing. So far, the data shows that a total of 1336 breath test were carried out containing 10688 breaths (8 per breath test). Around half the families (8) produced more than 100 breath tests each and the time of day they were completed showed a distinct bimodal distribution implying that they were able to get the child to do both morning and evening testing sessions. Further data analysis continues**.**



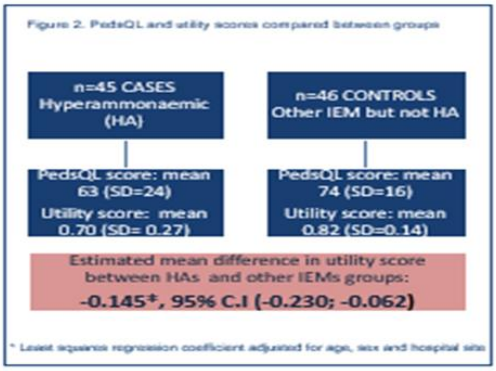
The frequency of the time of day the participants carried out the breath tests for those using machine numbers 8 and 9.

(iv) **Health Related QoL studies:** PedsQ4 and EQ-5D have established some important facts about Inborn errors of metabolism (IEMs) associated with hyperammonaemia. Children with HA have a significantly lower quality of life than those with other IEMs in all domains except emotional health. Especially low is social and school functioning. Overall the total score is 63 (SD=24) compared to 74 (SD=16) for other IEMs (Figure 1). In a study on a population of 'healthy' children the mean total score was 84.



(Figure1)

(v) Mapping children and young adults PedsQL scores to EQ-5D utility values (n=91, mean age 13 years) successfully allowed for estimation of utilities, which provides estimates for future economic evaluations in this population. Cases with HAs including UCDs had a mean utility score of 0.70, compared with other IEMs score 0.82. Healthy children of similar mean age scored on average 0.89 in a previous study (Verni JW et al. The PedsQLy* 4.0 as a Pediatric Population Health Measure: Feasibility, Reliability, and Validity. Ambulatory Pediatrics. 2003;3:329 341). The difference in utility score between the two groups, adjusted for age, sex and hospital, was -0.145 (95% C.I. -0.230; -0.062), meaning that if this difference had been extrapolated to a year spent in this health state, patients with HAs including UCDs would have decreased their survival by 53 fewer days of "perfect" health than patients with other IEMs. (Figure 2).



(Figure 2)

Finding of health care resource usage for families using AmBeR at home:

Seventeen families used the AmBeR device at home and were provided with daily diaries to complete either on paper or online, as preferred. Twelve families reported some daily data, most over a period of 3 months: five families reported over a period of four months. When completing online, some families double entered data on the same day. Of the twelve families who reported some daily data, seven reported contacts with health services on 27 different days in total, including two families who reported one 3-night admission to the hospital each, one due to vomiting and the other due to high ammonia levels. Due to the amount of missing or invalid data, it is not possible to estimate the full amount of health services used for families over the period, nor their costs to the NHS.

(vi) **Qualitative work in the Home Study:** A series of common themes emerged in the interviews:

a. Early diagnostic uncertainty in many cases with associated shock when diagnosis made and significant family stress
b. Food, eating patterns and diet becoming an over-riding element of daily family life
c. Having to be 'Always prepared' for emergency – "Like living with a time-bomb" affecting all parts of daily living leading to:
d. Social isolation of family
e. Being more 'Expert' in UCDs than most doctors causes problems with consultations (Families rarely consult their GPs for instance)
f. Transition to adult care a major challenge as compared to 'Children's Metabolic services' less personal, less appropriate for the young and less expertise.

Conclusions

The primary aim of this study was to examine the utility of a breath ammonia measuring device and sensor to reflect the user's blood ammonia. The device was able to be used by children although further refinements based on user feedback will need implementation. The major barrier to clinical utility is the actual ammonia sensor which does respond to ammonia in breath but not in a consistent, measurable and reproducible manner. Two elements are considered responsible for this poor reproducibility: variation in sensor thickness during production and changes in electrical properties such as resistance on storage and during calibration. One area worth exploring in terms of the latter problem is an internal calibration system within the breath ammonia collection device. The primary sensor production issue is likely the major determinant of irreproducibility and needs addressing initially. Overall, the device and sensor are not ready to be used in a clinical setting and considerably more time is required before becoming operational.

In terms of Urea Cycle Defects, we have demonstrated a clear patient and family mandate to continue work in this area. Whilst blood ammonia levels were often normal in our clinic study, these were single day measures and even then, three of 48 cases (~6%) had ammonia levels above 100µmol/L (>twice normal and to a degree neurotoxic). The quality of life data indicates that in all domains except emotional wellbeing, children with UCDs have a reduced quality of life compared to children with other inborn errors of metabolism and the general population of 'healthy' children. A novel aspect to our work has been to develop utility scores for UCDs and other IEMs. This will allow future interventions in this field to be assessed in terms of improvement in QALYs. The development of

utilities, to our knowledge is novel within childhood disorders. The lived experience of families with a member having a UCD captured in our qualitative research is also novel and can be used to inform future IEM NHS service developments.

Parent comments: 'Basically, it's a great idea, they need to develop industry strength sensors. I thought it was written well, in English, so a lay person could understand it, although even the technical bits were easy to understand.....'

11. Intellectual Property, Commercialisation and Clinical Adoption

Beyond Publications listed in the section above, please provide brief details of IP outputs arising from this research. The term 'IP outputs' refers to any tangible product of the research, not just academic publications. Outputs can include but are not limited to:

- Guidelines (clinical, service or otherwise);
- Copyright (e.g. questionnaires, training aids, toolkits, manuals, software, etc);
- New or improved design of medical devices or instrumentation;
- New or improved diagnostic;
- Trial data that could be used to support a CE mark, market authorisation or equivalent;
- Trial data that could be used to shape or influence a healthcare market or government;
- Potential new drug or healthcare intervention.

If these outputs are different to those anticipated at the start of the research, please briefly outline the reason for any changes.

If you filed any patents as a result of this research, please include the title, number, territories and the current status (pending, published, granted), and outline your further patent strategy, including key territories where protection will be sought. If you have conducted any freedom to operate searches, please describe the results and provide details on who carried them out and when, and explain whether or how they have influenced your research strategy.

Outline the ownership arrangements for the IP outputs arising from the research, and highlight any changes to the original plan. Describe the process by which the research will enter the healthcare environment, including how your IP outputs will be acknowledged, selected and introduced for use in the health and care service or wider society. Where possible consider how the work will be able to be adopted and implemented longer term. Please describe the proposed route to market (commercial or non-commercial) for your IP outputs. Describe who is needed to take it forward and the relationship you currently (or propose to) have with these parties. If your IP outputs are likely to be commercially exploitable, please include details on how you plan to develop this.

Consider what investment or support is be needed for the next steps in this research to maximise impact (e.g. from NIHR, other Government departments, charity or industry), and explain what such funding would enable.

Describe the difficulties which may be faced in generating impact from your research. These may be difficulties you will face yourself, or challenges faced by those in the implementing context (e.g. clinicians). For example:

a) Did the research use data, technology, materials or other inventions that are subject to any form of intellectual property protection (e.g. copyright, design rights, patents) or rights owned by another organisation(s)? If yes, provide brief details of how such third party IP was accessed (e.g. collaboration agreement, drug supply agreement) and any restrictions this may place on future research and/or dissemination/exploitation.
b) What are the key current and future barriers to uptake of any IP output directly in the health and care service, through commercial exploitation or other means, e.g. potential regulatory hurdles?
c) What are the challenges for getting your research implemented in terms of acceptability, accessibility and feasibility? How will you address these?

Please remember that you are contractually obliged to notify NIHR of any plans to enter into commercial agreements. *Please discuss any such plans with the appropriate support function at your institution (e.g. Technology Transfer Office or equivalent) (**1000 words**).*

The key intellectual property brought to the project was the Amber Sensor design and patent. During the research, no new innovations were developed around the sensor, including use, which was the single limiting factor in the project. From the outset, this was seen to be the most likely source of potential improved IP.

Another outcome associated with potential IP, but which did not produce any tangible IP was the user manual. The manual for device operation which was produced for focused use and user groups will change significantly with future device changes and user interactions. Manual contents were not copyrighted; No other outcomes were copyrighted;

The device design was redeveloped for specific use in the tests carried out. There was no trade secret requirement or opportunity due to the commercially available components used. The testing devices produced are not commercially viable.

Trial data produced could not be used in any specific or official CE or other device validation activity due to the variability in results from sensors. Data produced has value in advising future steps, but none is immediately addressable without further development related to sensor variability.

Should any IP remain with the trial data this value has not been realised to-date and is not expected to have any commercial value. Outcome value may come from scientific publication.

As was expected at the outset of the project, future development of sensors and associated device will be the only impetus that drive all new commercially viable innovation.

12. Actual and Anticipated Impact

Please provide a brief impact statement. This should describe the immediate impacts of the study, or the anticipated longer-term impacts, i.e. what has changed or what is likely to change as a result of the research and what will the benefit be, for example:

The AmBeR device to measure breath ammonia potentially can improve both management at home and in the clinical setting of Urea Cycle Defects. Parents have been unanimously positive about participation and device potential with patient/family input universally helpful. Quality of life measures are significantly reduced in this condition and it is possible to use paediatric specific general QoL questionnaires to map to health utilities to derive QALYs. Currently the sensor is of insufficient production reproducibility to commercialise AmBeR, but data generated in this study will allow us to improve future production and reliability

Describe the impact the research has already achieved or might achieve in the short, medium and long term.

This can include impact on current NHS priorities, clinical guidelines, patient benefit, service provision (for e.g. cost, staff time, hospital bed days, value for money etc), current practice, scientific advances and implications for policy.

Describe who has benefitted from the research activity. Clearly identify who or what user groups were affected as a result of this research. Where possible, give an indication of the size and scale of the different user groups (e.g. less than 1k, over 1m, etc).

Indicate the anticipated timescale for the impact(s) to reach patients/the NHS or the public, providing a quantitative estimate of the scale for these potential benefits, and the extent (e.g. local, national, regional) if possible.

Describe any wider mechanisms/approaches that were used to achieve impact, for example, knowledge engagement, knowledge translation, on-going dialogue with end users/stakeholders.

For research emphasising a clear trajectory into practice, it is important not to 'overclaim' and care should be taken to cover the limitations of the study and any risks associated with implementation.

This should be a comprehensive and realistic, stand-alone summary of the impact of the work. If you include health economic information, please specify the value of the QALY used.

Where actual impact has been achieved, please provide evidence.

NOTE: Negative, definitive findings that could inform disinvestment are also of value. (***750 words***)

Significant progress to providing a solution to sufferers of hyperammonaemic disorders has been made, particularly in relation to the technological development of the breath system platforms. These were rigorously assessed in both multi-centre clinical and home environments, which demonstrated their operational utility in both settings. This has provided a foundation for further progress, which focuses on demonstrating sensor production performance reliability. The study has determined where future activity must be focused to allow it to continue to move towards the original objective. In the immediate future, activity will focus on addressing these remaining technological issues, to allow the technology to be re-evaluated again in this patient cohort, as well as in other areas of interest to emerge, such as chronic liver disease, and *H. pylori* diagnosis. We estimate, with immediate financial support, that outstanding technological issues can be resolved in 2 years, with a large-scale clinical evaluation at all 7 major IEM UK centres to follow.

On a broader plain, this study has brought together four of the seven UK IEM sites to work collaboratively to achieve extremely good recruitment to the study and data collection. This collaboration might serve future studies well in this 'niche' research area. For families with this 'rare disease' the fact that NIHR is funding the study is important indicating NIHR's desire to include rare disease studies. The PPI involvement and recruitment figures suggest the families valued this study for its potential for their children but also for acknowledging a disease that rarely attracts much research attention (the QoL data is unique across the world).

This study also confirms that we now have good methods in place to estimate QALYs for children (with obviously all the caveats inherent to what a QALY is) and that we have shown that it is possible to use paediatric specific general QoL questionnaires to map to health utilities to derive QALYs. Our successful application of this method has been noted by the Health Economics community, inviting us to present an oral presentation of the study findings at a trial methodology conference.

13. Dissemination

NIHR is keen that the findings of the research it funds are disseminated effectively to patients, the public, the NHS and the healthcare and research communities.

1. Please describe how you have disseminated your research findings and what your plans for further dissemination are. Describe your publication strategy (note that individual peer-reviewed publications will need to be listed under Section 12) and describe any major communication and public engagement activities here, including academic workshops and conference presentations, feedback to research participants, meetings or discussions with policymakers or healthcare professionals, and media coverage (***450 words***). Findings were presented at 3 international conferences as posters or oral communications

a) Society for Inherited metabolic Disease, Seattle, USA April 2019
b) Society for the Study of Inherited Errors of Metabolism, Rotterdam, Netherlands. September 2019
c) International Clinical Trials Methodology Conference, Brighton, UK. October 2019

2. Findings were presented at Metabolic Support UK meetings whilst the project was underway. Preliminary final results were presented at a meeting on 12th October 2019 by Julian Hamilton-Shield and Joanna White.
3. A newsletter was sent to all PPIAG members updating them on the study progress and preliminary findings in 2018
4. Findings were presented to members of the PPIAG, NIHR and members of the AmBeR Management Group throughout the study.
5. ITN recorded a film for the Society of Biology about the AmBeR Study in September 2019
6. Results will be presented to at the British Dietetic Association Annual Research Meeting in December 2019

Plans for further dissemination include peer- reviewed publications

14. Publications

Number Published		Number in press		Number submitted		Number in preparation	2

Please provide a link or list here any peer reviewed journal publications which have resulted from the work; forthcoming items should also be included. Please also detail any awards and/or prizes received by the team as a result of undertaking the research.

NOTE: *You are contractually obliged to send one draft copy of the proposed publication to the Authority's Representative at the same time as submission for publication or at least 28 days before the date intended for publication, whichever is earlier. Any published paper directly associated with your award must comply with the NIHR Open Access policy and be made freely available.*

All publications must include the following funding statement:

*"This report is independent research funded by the National Institute for Health Research (*Invention for innovation, "Evaluation and validation of a breath ammonia measurement technology for the improved management of patients with urea cycle defects" and II-LB-0315-20006*). The views expressed in this publication are those of the author(s) and not necessarily those of the National Institute for Health Research or the Department of Health and Social Care"*

Manuscripts in preparation

1. Health Related Quality of Life in patients with hyperammonaemic disorders. Target journal. Pediatrics

2. Family experiences of living with a Urea Cycle Defect: findings from the AmBeR qualitative study. Target journal. Journal of Inherited Metabolic Disease.

15. Patient and Public Involvement

Aim
The PPI in this study aimed to confirm the relevance of the technology, guide the study approach to confirm and enhance its appropriateness, and ensure the potential benefits of the study to the public are fully realised

Methods
The approach to PPI employed in this study pivoted around a Patient and Public Involvement Advisory Group (PPIAG) which included patients and their carers. Recruitment to this group was facilitated by Metabolic Support UK (formerly Children Living with a Metabolic Condition; CLIMB), which also hosted two PPIAG meetings at its national conference. Given the geographical spread of families affected by

UCDs, and potential difficulties travelling to Bristol on a specific date, we established an enlarged, virtual PPIAG. Members of this group were invited to all face-to-face PPIAG meetings and were also consulted virtually at various points by e-mail regarding the study plan and outputs. Measures were put in place to update the PPIAG on the impacts of their involvement. In addition, representatives of several families affected by a UCD regularly attended project Steering Group meetings (two to four representatives). PPIAG members are invited to contribute to co-author the publication emerging from the qualitative study of families' experiences of living with a UCD.

Study results

Discussions with patients and carers at the pre-proposal phase, facilitated by Metabolic Support UK, confirmed interest in the AmBeR device and its potential impact on families. The virtual PPIAG included 19 families. Face-to-face PPIAG meeting resulted in important suggestions for improving the AmBeR prototype device for hospital and home testing, particularly in terms of its technical accessibility and in engaging young children while they were blowing into the device. Feedback was given on study patient information leaflets and consent forms before ethics submission. A further PPI meeting held in October 2017 at the Metabolic Support UK conference, combined with e-mail consultation with the virtual PPIAG group resulted in advised changes to the health economics and qualitative study protocols, the planned approach of the dietary intake log and improvements to the home study protocol. Feedback from families challenged some assumptions implicit in both the quantitative and qualitative questionnaire guides, providing crucial insight into the fundamental impact of living with a UCD on parental employment, for example, and the range of physical and social impacts presented by the condition. PPIAG feedback on the home testing protocol resulted in significant changes to the language and structure of the explanations of the AmBeR device at home. The protocol document thus contained comprehensible information complementing hands-on training more effectively.

Discussion and conclusions

PPI activities had an invaluable impact on the study: confirming its overall value, providing detailed guidance to enhance accessibility and appropriateness of all study materials. Some of the feedback regarding technical aspects of the prototype device (e.g. attractiveness of the device box and size of coloured light panels) was too late to be put into practice for this project, as these basic elements of the prototype had already been established and manufactured. This suggests that PPI in the nascent stages of prototype development might have had an important early impact.

Reflective/critical perspective

The PPI in this study generally went well. Regular communications were exchanged with the PPIAG and the facilitating organisation (Metabolic Support UK), including a detailed study update circulated in late 2018. More systematic communication might have been advisable, if only to explain the extended timeline of the project and manage expectations of study progress and outcomes. During the project the PPI lead and her colleagues on the People and Health West of England (PHWE) PPI Learning and Development programme consolidated new tools for logging and sharing PPI activities and impacts. Some of these tools would be appropriate for any future study of this type to streamline communication and monitor impacts.

UCDs disproportionately affect the South Asian community in the UK, and this community experiences relative marginalization in terms of healthcare access, as well as currently being poorly represented in PPI. Only two of the 19 families in the PPIAG group were from a South Asian background. It would be appropriate to proactively recruit affected families from this community as members of the PPIAG for future studies of this type, as well as working to ensure their involvement in project Steering Groups. Additional resources might be required to work more closely with this community and support their participation in PPI.

☒	Please tick the box if this section of the report has been written with members of the public who have been involved in the research.

16. Future Research Plans

Please outline your next steps to maximise patient benefit or to further inform policy development/evaluation. If further research and development is needed, such as a definitive trial following a feasibility study, or a programme grant following preparatory work, include details on the likely funder and timetable for submission. If the output(s) from your research are largely commercial, describe the proposed route to market in Section 13 above.

If no further plans are thought necessary, please explain why this is the case (***750 words***).

Further research will focus immediately on the technical issues relating to ammonia sensor production, calibration and storage stability. This is being pursued primarily through application to Innovate UK in collaboration with the Bristol clinical team. This programme allowed the identification and clarification of these issues, and how they can be addressed

17. Publication of Research Findings

The NIHR is committed to making the findings of the research that it funds publicly available. This report or sections thereof, in particular the scientific and plain English summaries, may be published, considering confidential and commercially sensitive information. We may wish to use the content of this form for contents on our website, to illustrate the work we have funded, share good practice, and make information about research more accessible to the public.

Please indicate if there is any information that you do not wish us to place in the public domain and explain why (***500 words***).

Outputs from the project relating to the performance of the AmBeR devices, and the clinical and home study breath measurement data obtained should not be published. The remaining technical challenges are of a commercially sensitive nature, and such information would impact negatively on Breath Dx business activities. Similarly, the data generated during the clinical studies is not yet considered reliable to allow a claim of either the existence, or lack of a correlation between breath and blood ammonia, or a relationship between patient health status and breath ammonia levels. Published outputs should be limited to other aspects such as the qualitative and quality of life data.

18. Data Sharing

Making clinical data sets available to investigators beyond the original research team can improve patient care, advance medical knowledge and provide better value for money from health research.

Data generated through participation of patients and the public should be put to maximum use by the research community and, whenever possible, translated to deliver patient benefit. Data sharing benefits numerous research-related activities: reproducing analyses; testing secondary hypotheses; developing and evaluating novel statistical methods; teaching; aiding design of future trials; meta-analyses; and helping to prevent error, fraud and selective reporting.

Data sharing achieves many important goals for the scientific community, such as:

- Reinforcing open scientific inquiry.
- Encouraging diversity of analysis and opinion.
- Promoting new research, testing of new or alternative hypotheses and methods of analysis.
- Supporting studies on data collection methods and measurement.
- Facilitating education of new researchers.

Where applicable, please provide a statement about your data sharing and accessibility. It should provide a clear and positive indication:

- Where and when the data will be shared;
- Who can access the data:
- How the data can be obtained (***250 words***).

- **Where and when the data will be shared?**

The data is currently stored on the University of Bristol's SQL servers.

Once any processing/in-house analysis is complete the data will be exported from the SQL databases and stored on the University of Bristol's Research Data Storage Facility (RDSF). Any (non-identifiable) data can be easily shared and will be supplied in csv or any Excel compatible formats either via email, the RDSF data sharing facility or a file sharing service.

- **Who can access the data?**

Non-commercially sensitive data will be available for other researchers on request once publications have been accepted on quality of life and qualitative interviews have been published.

- **How the data can be obtained?**

Data stored on the RDSF is indexed and details of what is available will be listed on the University of Bristol's data.bris research data repository. This service provides a search functionality for research data and returns contact details for the data custodian.
Once contacted the data custodian will then liaise with the interested parties to arrange any data transfer.

19. Post-Award Monitoring

Please be aware that all NIHR-funded research will be followed up for a period of five years after project completion. Your NIHR Programme Manager will contact you to agree a post-award monitoring plan, including the process and timelines. Our aim is to collect information about further research and development, any further funding obtained, commercialisation, publication and dissemination plans, and any impact achieved.

Please provide the name, address, phone number and email of the individual whom we can contact for post-award monitoring of this project. Usually this will be the Chief Investigator, however, another individual, for example a project manager, may be named instead.

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