DEFINING THE PHENOTYPE IN ALSTROM SYNDROME AND RELATED GENETIC AND CELL CULTURE STUDIES (DAS)

Short title: INSIGHT INTO ALSTRÖM SYNDROME

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Preface

This protocol for the Defining Alström Syndrome (DAS) study describes the background, design and organisation of the study. The protocol will be maintained by the Study Coordinating Centre at Torbay Hospital over the course of the study through new releases of the entire protocol, or issues of updates either in the form of revisions of complete chapters or pages thereof, or in the form of supplemental protocol memoranda.

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1.0 PROTOCOL SYNOPSIS

This is a UK-wide, prospective cohort study of children and adults with Alström syndrome, characterised by anthropometry, biomarkers and co-morbidities. The tight clinical characterisation will allow comprehensive identification of complications and provision of management pathways. This will involve identification of risk factors for cardiac hepatic and renal disease; audit of effects of established therapies and lifestyle interventions including evaluation of glycaemic and weight control; and enrolment into future clinical trials. In addition it will allow us to relate phenotype to genotype, and to generate a tissue resource for laboratory based mechanistic studies to understand the aetiology of the syndrome.

The overall objective of this study is to characterise a cohort of children and adults with Alström syndrome. This will include baseline and repeated assessments over time of the anthropometric, cardiovascular, orthopaedic, metabolic and emotional status of individuals with Alström syndrome, mutation analysis and collection of tissues in order to:

- Describe the natural history of Alström syndrome and related co-morbidities in a multiethnic cohort of UK children and adults with the syndrome
- Identify surrogate markers (genetic, metabolic, imaging) which will predict progression of the syndrome
- Characterise the cohort in terms of biomarkers needed to monitor the effectiveness of future planned intervention studies to prevent or delay the progress of the syndrome
- Generate a tissue resource for basic science studies into the biology of the syndrome

The study is divided into two phases:

- Baseline characterisation (Phase 1)
- Follow-up risk assessments (Phase 2)

**Phase 1** involves screening for Alström syndrome (and exclusion of other diagnoses), DNA and tissue (skin biopsy) collection. Patients will be asked to consent for clinical and genetic data to be stored on an anonymised secure database. Individuals who fulfil agreed minimum diagnostic criteria (cone-rod dystrophy plus one of: obesity, diabetes, hypertriglyceridaemia, cardiomyopathy) will be eligible for entry.

**Phase 2** will involve repeated measures over time (follow-up risk assessments at annual review clinics). They will be seen at annual intervals until the end of the study (3 years).

During each phase of the study, residual blood samples (and DNA samples in Phase1) from consenting participants will be stored indefinitely at a core laboratory for future metabolic assessments that bear upon the mechanisms of disease. This resource will also be used to study genetic
and metabolic characteristics associated with the development of diabetes and obesity in the general population. Patients may still participate in all phases of the study even if they choose not to give consent for DNA or tissue storage.

Participants will be recruited through the patient support group, referring physicians and paediatricians and other health professionals. They (and their parents or guardians if children) will be asked to attend a National Alström medical clinic to go through the information sheet with a research nurse, and to gain consent to take part. For children, information sheets will be provided in suitable language and they will be asked to give their assent. They will not be allowed to enter the study unless parental consent is obtained. There will be one consent that covers both phases of the study.

The primary outcome is the detailed genetic anthropometric and metabolic phenotyping of the cohort together with identification of surrogate markers for disease progression, complications and monitoring of future therapies.

2.0 INTRODUCTION

Alström syndrome is a rare monogenic syndrome characterised by early onset blindness and obesity (1). In addition to the blindness, deafness obesity and insulin resistance originally described, cardiomyopathy, hyperlipidaemia, renal failure, hepatic fibrosis, and smooth muscle dysfunction have been reported (2, 3, 4, 5, 6, 7) with unexpected lack of diabetic peripheral neuropathy in patients with long standing diabetes (8). The syndrome is caused by loss of function mutations in ALMS1, encoding a protein of unknown function (9). Alström syndrome is inherited as an autosomal recessive condition, so that it disproportionately affects populations with a high prevalence of consanguineous marriages (10). Differing severity of complications may link with particular mutations in the ALMS1 gene (11). Development of cardiac hepatic and renal fibrosis is increasingly recognised as one of the consequences of insulin resistance and type 2 diabetes in the general population. Alström syndrome is an extreme paradigm for these conditions. It is likely that understanding of the mechanisms of organ damage in the latter will provide insights into the former common conditions.

The syndrome has been described in over 600 families worldwide, and 50 in the UK. Genetic confirmation has been ascertained in approx 90% so far. The condition is first apparent as photophobia, nystagmus, leading to progressive visual loss from childhood. Obesity, insulin resistance, and partial nerve deafness follow, then type 2 diabetes(80%), severely high blood triglycerides(7), cardiomyopathy (50%, with more than 25%
affected in infancy and renal failure (6). A smaller number also develop incoordination of swallowing and dysynnergy of the bladder resulting in incontinence. Some patients develop thickening of the spine. From 1998 the patient support group Alström Syndrome UK has worked with staff of Torbay Hospital to review UK subjects with the syndrome and plan best therapy for them in conjunction with their local medical care teams. In 2006 the National Commissioning Service for rare disorders (NCG, formerly NSCAG) funded adult clinics at Torbay hospital and children’s clinics at Birmingham Children’s Hospital. This has allowed identification and confirmation of a wide range of complications and potential treatments in the disorder (11-18). It has been possible to audit treatments and make information available on the web site www.alstrom.org.uk. This protocol aims to undertake a more systematic investigation of patients with the syndrome in order to characterise it more completely.

3.0 OBJECTIVES:

The primary objective is patient benefit through improving the quality of life of people affected by Alström syndrome. This will be achieved through detailed characterisation of a cohort of children and adults affected by the syndrome leading to earlier diagnosis and improved treatments.

The Secondary objectives are to:

- Describe the natural history of Alström syndrome and related co-morbidities in a multiethnic cohort of UK children and adults with the syndrome
- Identify surrogate markers (genetic, metabolic, imaging) which will predict progression of the syndrome
- Characterise the cohort in terms of biomarkers needed to monitor the effectiveness of future planned intervention studies to prevent or delay the progress of the syndrome.
- Generate a tissue resource for basic science studies into the biology of the syndrome.
- Establish a data base of genetic, clinical and metabolic characteristics of participants to facilitate analysis of genotype phenotype correlations.

4.0 RATIONALE

This study is made possible by the generosity and leadership of Alström Syndrome UK and its family members that have led to the establishment of National Commissioning Group funded clinics for adults in Torbay Hospital and children in Birmingham Children’s Hospital. The project is
financed by a Big Lottery Research grant awarded to ASUK whose family members have been involved at every stage of planning the clinics and developing the research protocol. Participants for the study can thus be recruited largely from existing funded clinics. In addition, raising awareness of the syndrome in the blind community is likely to uncover as yet undiagnosed families; (conservative estimate up to 50).

We anticipate that this study will lead to the following gains in understanding of the syndrome:

1) Identifying the full extent of co-morbidities in the syndrome, and evaluation of efficacy of established therapies in their treatment.
2) Discovery of any relation of site and type of mutations with individual complications
3) Explanation of effects of ALMS1 protein malformations on function of patient derived cell lines in culture.
4) Increased understanding of mechanisms causing insulin resistance, fibrosis in cardiomyopathy, renal disorders and fibrosis of the liver in the wider population.
5) Improved disease prognosis will result from characterising the phenotype and correlating this with individual genotypes.

5.0 STUDY OVERVIEW

This is a 3 year prospective observational (non-intervention) study designed to systematically define the occurrence, severity, and progression of co-morbidities in people affected by Alström syndrome. Data will be stored on a secure database to accommodate all anonymised study information. This will be used to analyse phenotype genotype correlations, store information on biomarkers, and monitor response to clinically indicated treatment.

5.1 Inclusion criteria
1. Genetically confirmed diagnosis of Alström syndrome.
2. Clinical diagnosis of Alström syndrome. This requires the presence of retinal dystrophy and one of the following: obesity, diabetes, cardiomyopathy or high lipids (triglycerides); see Appendix 2.
3. Children and adults under investigation for unexplained cardiomyopathy, retinal dystrophy, or severe insulin resistance, particularly where two of these features occur together even if retinal dystrophy is not present. This to ensure mild forms of the syndrome are not missed.
4. Patients will be recruited from birth. There is no upper age limit.
5. Willingness to take part in study
6. Capacity to give informed consent to procedures and treatments.
5.2 Exclusion Criteria
1. Lack of capacity to consent to procedures
2. Other known monogenic cause of type 2 diabetes (MODY, Prader Willi syndrome, LMBBS, Friedreich's Ataxia)

5.3 Phase 1
This involves screening for Alström syndrome (and exclusion of other diagnoses), DNA and tissue (skin biopsy) collection. Participants will be asked to consent for clinical data being stored on an anonymised secure database. The purpose of DNA collection at this stage is to undertake Alström gene mutation analysis. DNA will be retained for further analysis where only one pathological mutation has been discovered, for further investigation of the ALMS1 gene and for possible subsequent identification of modifier genes.

The skin biopsies will be used to establish immortalised cell lines from patients with known mutations. Participants will then be invited to undergo baseline assessments of neuropathy, test meal studies to assess metabolic and hormonal responses to diet; cardiovascular imaging studies, (carotid intima media artery thickness, arterial stiffness, pulsewave velocity and tissue Doppler); and prospective audit of the effects of therapiess for co-morbidities. In addition participants will be invited to provide 24hr urine samples for measurement of steroid metabolites.

It is crucial to ensure that milder forms of the condition are included. This requires three separate approaches to genetic testing:

1) Participants in whom diagnosis of the syndrome has already been confirmed by ALMS1 gene testing. No further genetic testing required.
2) Subjects with retinal dystrophy and one of obesity, diabetes, cardiomyopathy or hypertriglyceridaemia. Genetic testing is clinically indicated, so DNA samples will be sent for ALMS1 mutation analysis as part of the routine clinical service. We will perform vascular and metabolic tests to complete characterisation of their phenotypes. If ALMS1 mutations are detected, then these patients will be invited to complete phase 1 and progress to phase 2 of the study.
3) Patients who present some features of Alström syndrome but no or mild retinal dystrophy. We will request a DNA sample as a research investigation to identify atypical or mild forms of the syndrome. If no ALMS1 mutations are identified, these patients will not be followed up further in this study. If mutations found they will complete phase 1 investigations and progress to phase 2.
5.4 Phase 2

Phase 2 will involve repeated measures over time (follow-up risk assessments at annual review clinics). Patients will be seen at annual intervals until the end of the study (3 years). At each review metabolic and cardiovascular studies will be repeated resources permitting.

During each phase of the study, residual blood samples (and DNA samples in Phase 1) from consenting participants will be stored indefinitely at a core laboratory for future metabolic assessments that bear upon the mechanisms of disease; and to obtain additional genetic and metabolic information about biomarkers associated with the development of diabetes and obesity in the general population. Patients may still participate in all other phases of the study even if they choose not to give consent for DNA or tissue storage.

6.0 STUDY PROCEDURES

6.1 Phase 1

In Phase 1, patients will be approached by the study researchers and a detailed clinical history and examination will be undertaken. This is part of the routine clinical management of the syndrome. Patients will be asked consent to include this data and information from their medical records, in the anonymised database.

Families and carers of deceased patients with the syndrome will be asked for permission to review records and case notes and invited to participate in a questionnaire about family medical history to add to our understanding of the condition.

6.1.1 Non-study procedures that are part of routine clinical care

The following are clinically indicated investigations that will be undertaken as part of routine medical care. The results will be included in the research database.

- Early morning urine sample for albumin creatinine ratio
- Hepatic: plasma samples for liver function tests; Doppler ultrasound if clinical suspicion of portal hypertension
- Endocrinology: thyroid, sex and pituitary hormones
- Haematology: full blood count
- Audiogram
- Cardiac: Echocardiogram, ECG, cardiac MRI if available
- Insulin resistance/diabetes: Annual assessment of capillary blood glucose monitoring to identify development of glucose intolerance; Regular assessment of glycated haemoglobin (3-4 monthly) to diagnose diabetes and to monitor therapy; assessment for peripheral neuropathy.
Hyperlipidaemia: Annual full lipid profile. Patients will be fasted overnight for this test.
Mutation analysis of ALMS1 gene if fulfils clinical criteria for Alström syndrome

6.1.2 Study procedures that are for research and not part of routine clinical care
The following are research procedures that Alström syndrome patients will be invited to undergo, and are not part of routine clinical care:-

Patients will be invited to attend in the morning having fasted overnight and not consumed any liquids apart from water. Patients will then be offered a breakfast (‘the Mixed Meal Tolerance test’). Blood sampling will be undertaken at 0, 30, 60, 90 and 120 minutes through an indwelling cannula (this is a tiny plastic tube left in the vein to allow repeated blood samples to be taken).
- Blood will be assayed for the following: Serum Apoproteins B, C and E lipoprotein phenotype; serum leptin; GLP1; stimulated insulin and C-peptide.

Other investigations to be undertaken:
- Renal: serum aldosterone, renin glomerular filtration rate
- Hepatic: fibrotest, fibroscan
- Cardiac: plasma pro-NT BNP, high sensitivity CRP and high sensitivity Troponin; Carotid intima media thickness; pulse wave analysis and augmentation index. Measurement of cardiovascular autonomic function
- Patients of all ages will be asked to provide a 24hr urine collection to be tested for urine full steroid metabolite profile
- Postprandial urine collection for C-peptide;

Other research investigations:
- USS scan parotid gland on selected patients with symptoms of excess fat deposition (Adults only);
- Blood for DNA extraction and mutation analysis (patients with atypical features of Alström syndrome); banking of saved plasma (tissue bank) and urine
- Skin biopsy for fibroblast culture
- Questionnaire for next of kin of deceased patients with Alström syndrome including request for pathology specimens for review from licensed tissue bank authority.

6.2 Phase 2
In Phase 2, the following research investigations will be repeated annually for the 3 years of the study:
Patients will be invited to attend in the morning having fasted overnight and not consumed any liquids apart from water. Patients will then be offered a breakfast ('the Mixed Meal test'), and 2 hours later the following samples will be collected and investigations undertaken:

- Renal: serum aldosterone, renin glomerular filtration rate
- Hepatic: fibrotest, fibroscan
- Cardiac: plasma pro-NT BNP; Carotid intima media thickness; pulse wave analysis autonomic function and augmentation index. Measurement of cardiovascular autonomic function
- Metabolic: Serum for Apoproteins B, C and E lipoprotein phenotype; Postprandial urine collection for C-peptide; stimulated insulin and C-peptide.

Other research investigations:

- USS scan parotid gland on selected patients with symptoms of excess fat deposition (Adults only);

6.3 Detailed methods

6.3.1 Arterial stiffness and central pressure measurements

The techniques of pulse wave analysis (PWA) and aortic pulse wave velocity (PWV) will be used. Arterial stiffness and central aortic pressure may be measured non-invasively by the technique of pulse wave analysis (PWA) using the Sphygmocor apparatus (BPAS-1; PWV Medical, Sydney, Australia) as developed by O’Rourke. With PWA, measurements are taken from the radial artery at the wrist using a micro manometer (SPC-301; Millar Instruments, TX, USA) applying the principle of applanation tonometry to flatten the artery by gentle pressure. Data are collected directly into a desktop computer and processed by the system software to allow accurate on-line recording of the radial artery waveform. The operator visually assesses the waveform to ensure that the best possible waveform is recorded. The corresponding aortic pressure waveform can then be generated from an averaged radial artery waveform (derived from 20 sequentially recorded radial artery waveforms) using a validated transfer factor. Computerised analysis of the central waveform allows determination of several haemodynamic parameters including central aortic blood pressure and the augmentation index (AIx) a measure of pressure wave reflections within the arterial tree. The AIx is defined as the difference between the first and second peaks of the central arterial waveform, expressed as a percentage of the pulse pressure and is a measure of systemic arterial stiffness.

Aortic PWV is determined by recording pressure waveforms at 2 sites sequentially; carotid-femoral for aortic PWV and carotid-radial for brachial PWV. Wave transit time is calculated by the system software, using the R wave of a simultaneously recorded ECG as a reference frame. Surface
distance between the 2 recording sites is then measured, thus allowing PWV to be measured.

Radial blood pressure is calibrated against brachial blood pressure, which is measured using an Omron automated sphygmomanometer (HEM-705CP; Omron Corporation, Japan).

6.3.2 Autonomic function testing
Cardiovascular autonomic nerve function will be assessed by ECG monitoring and determination of R–R interval using standardised techniques in response to deep breathing (heart rate changes over 1min of deep breathing at 6 breaths per minute – difference between maximum and minimum heart rates and heart rate changes during Valsalva). The effect of posture on blood pressure will also be recorded.

6.3.3 Carotid Intima Media Thickness (IMT)
Measurement of carotid IMT is established as a predictive maker of early atherosclerosis with several large epidemiological studies demonstrating that increased IMT predicts the development of coronary disease and stroke.

IMT is assessed using a high-resolution (>7.5MHz) ultrasound transducer coupled with wall-tracking software (Sonosite). B-mode images of the left and right common carotid artery are obtained with the patients in the reclined position.

6.3.4 Skin Biopsy:
The technique for skin biopsy is as follows:

1) Select site for biopsy-usually flank or medial aspect of forearm (adults); posterior aspect of upper arm (children).
2) Use sterile technique and swab skin with alcohol.
3) Infiltrate skin with 5ml 1% xylocaine/adrenaline/lignocaine with syringe using 5mm needle.
4) Insert punch to hilt with steady pressure and rotary movement. Use 4mm or 6 mm punch biopsy needle.
5) Remove specimen from punch with toothed forceps, drop in culture medium.
6) Close with 2-3 interrupted sutures (Ethilon 4/0 or 5/0) In children, steri-strips will be used to close the wound.
7) Apply Polyfax antiseptic ointment then Opsite or appropriate dressing.
8) Remove sutures or dressing at 5-7 days.

This procedure will be undertaken by a nurse or doctor trained in the procedure.
6.3.5 Foot examination
Research grade 2, 4, 6, 8, 10, and 15 gm monofilaments, (Bailey Instruments, Ltd., Manchester, UK) and neuroesthesiometer are used to test for protective sensation in subjects with eyes closed as previously described (13). Calloused areas are avoided-the fibre applied to the closest area of non calloused skin. Vibration perception threshold at the pulp of the first toe is recorded as mean of three tests. . Diagnosis of peripheral neuropathy is made when two of the following are present; vibration perception threshold >25Volts, loss of 1 or more 10 gram monofilament test responses, or typical neuropathic symptoms.

7.0 DATA COLLECTION AND STORAGE
Data will be collected at established clinics. Clinical information relevant to a patient’s ongoing treatment will be kept in their NHS records as is usual clinical practice. In the case of information for research purposes some data will be extracted from NHS medical records but all patients’ identifiers will be removed (the participant’s name will be replaced by a unique reference number known only to clinic staff and the individual participant) before being transferred to a dedicated research data base housed at Birmingham Children’s Hospital. Access to this database will be through a secure password protected web link and all stored data will be protected and backed up according to normal NHS procedures. A full list of participant names and reference numbers will be kept separately by the chief investigator. Any paper records of tests or results not included in the normal NHS patient file will be kept in locked storage facilities at Torbay or Birmingham and will be used to provide an audit trail and as a last resort back up to the database. Electronic or hard copy of echocardiograms, ultrasound, Xrays, MRI scans, and other complex imaging will not be transferred to the data base but may be reviewed as anonymised evidence if required to evaluate organ dysfunction. Written reports of these procedures will be held anonymised, on the data base.

8.0 OUTCOMES EVALUATION
8.1 Primary Outcome
The primary outcome is the detailed anthropometric and metabolic phenotyping of the cohort together with identification of surrogate markers for disease progression, complications and monitoring of future therapies.

The purpose is to create a resource of patient data for establishing the natural history and genotype phenotype correlations to inform clinical management.
8.2 Secondary Outcomes
The secondary outcomes are related to the phenotyping of the cohort:

- Quantification of pancreatic beta cell insulin reserve
- Quantification of HOMA analysis of tissue insulin resistance
- Assessment of glycaemic control estimated by measurement of HbA1c
- Characterisation of anthropometric variables and body composition
- Determination of metabolic variables including liver, renal and hormonal parameters
- Determination of cardiovascular disease risk variables including blood pressure, carotid intima media ultrasound, cardiac MRI
- Storage of DNA, fibroblasts, and other samples for identification of disease gene alleles and immortalisation of cell lines. Other tissue samples to include plasma and urine to be stored in an accredited tissue bank.

9.0 STATISTICAL ANALYSES
The main purpose of this study is to create a resource of patients with confirmed Alström syndrome that can be recruited into multi-centre intervention studies. Analyses of study data will be conducted to address the primary and secondary objectives of the study, other stated objectives, and other interrelationships among elements of study data of interest to the investigators and of relevance to the objectives of the study.

Participant characteristics, demographics, medical/diabetes histories, and other baseline measurements will be summarized for purposes of characterising the study populations and assessing overall cardiovascular risk characteristics. Descriptive statistics, including mean, standard deviation, median, range, frequency distributions etc as appropriate, will be presented for the overall population and for any risk cohorts identified. A secondary aim of the study is to prospectively determine the risk for cardiovascular disease and other co-morbidities using different measures. We will use echocardiographic findings and carotid intima media thickness above published cut-offs as surrogate endpoint markers for future cardiovascular disease risk. We will use proportional hazards regression models using (a) the percentage fat mass or BMI from body composition studies or anthropometry as a time-dependent covariate, (b) hypertension as a time-dependent covariate, (c) raised LDL-cholesterol or lowered HDL-cholesterol as time-dependent covariates. Adjustment for other covariates as indicated above will be performed.

9.1 Sample Size
We estimate there are about 80 affected patients in the UK, of whom we hope to recruit 60 to this study. 30% of patients are children. As this is an extremely rare disease, we will be able to undertake descriptive analysis,
but the study is unlikely to be powered to demonstrate significant differences with control groups such as healthy people, or people with type 2 diabetes in all of the outcome measures.

**10.0 ETHICS AND HUMAN SUBJECTS**

The average age at death in Alström syndrome is 20yrs, reduced because of infant death from treatable but unrecognised heart failure and adolescent onset cardio renal failure. However some subjects suffer less severe problems and can survive up to at least 58 years of age. It has been crucial to fully involve Alström patients and their families in planning of these studies, in particular explaining that effective control of blood glucose with Metformin, incretins, low carbohydrate diet and of hypertriglyceridaemia with Niaspan has to be carefully monitored to ensure that no adverse cardiac or renal effects occur. Similarly the patients will be involved in planning the testing of inhibition of the renin angiotensin system to protect heart and kidneys without causing very dramatic blood pressure falls and extreme creatinine increases.

Evaluation of changes in the adults may help us detect risk early in childhood; we would like to introduce some therapies on a clinically indicated basis and generate the evidence for or against effectiveness. These might include dietary or medicinal measures.

It is important to confirm diagnosis genetically in those taking part in the study. An 90% ascertainment of referred subjects has been attained and is improving. However results have to be discussed carefully with families and their carers especially if a phenotype-genotype correlation emerges.

Careful discussion of the precise nature of studies of DNA and pluripotent stem cells derived from skin biopsies will be necessary. It is hoped that earlier but more precise indications for major organ transplant will emerge from these studies. This will require thoughtful counselling.

Informed consent will be sought with Braille and voice mail adapted information given one week before signature. In children, parental consent will be obtained. This will cover:

- Clinical measurements outlined above, and data base of information.
- Collection of blood for DNA analysis where necessary
- Skin biopsy for tissue studies.
- Explanation of purpose and use of stored samples and clinical data. This information will be anonymised and shared with other approved researchers.

A project oversight committee has been set up by Alström Syndrome UK composed of respected academic and independent researchers and representatives of patients and carers. A separate management team will
be set up to oversee and control the Birmingham database and the Cambridge tissue bank. This will be composed of one member from each partner organisation plus one member from the oversight committee. It is expected that both the committee and the management team will meet at least twice per year.

Patients/families are free to withdraw their participation without disclosing the reason and without prejudice to their future care. The studies will be conducted in accordance with GCP Trust and MHRA guidelines.

11.0 STUDY SAMPLES

Patient DNA will be investigated and stored in The Department of Medical and Molecular Genetics, School of Clinical and Experimental Medicine, University of Birmingham, and Regional Genetics Department, Birmingham Women’s Hospital as part of their clinical care.

Skin biopsies will be studied and cell lines created and stored in The Institute of Metabolic Science, University of Cambridge. We will request permission for any excess tissue (plasma) to be stored in the HTA licensed Human Tissue Bank, University of Birmingham.

12.0 RESPONSIBILITIES:

TORBAY HOSPITAL (SDHCFT) is the sponsoring authority for this application and will provide for clinical care and investigation of Alström adult patients led by Dr R B Paisey

BIRMINGHAM CHILDREN’S HOSPITAL will provide for clinical care and investigation of Alström Children led by Professor Tim Barrett and will support a new study database containing anonymised patient information.

CAMBRIDGE UNIVERSITY Institute of Metabolic Science will store, manage and safeguard the Alström skin biopsies. Using these samples, Dr Robert Semple will lead a linked project (with existing ethics approval - Cambridge Research Ethics Committee REC No 06/Q0108/373), in which he will investigate the cell biology. The University of Birmingham will store, manage and safeguard Alström DNA samples.
13.0 REFERENCES


## APPENDIX 1: STUDY SCHEDULE

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<th>Phase 1 Baseline</th>
<th>Phase 2 12 months</th>
<th>24 months</th>
<th>36 months</th>
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<tr>
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<td>Follow-up assessment</td>
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APPENDIX 2: CRITERIA FOR ALMS1 GENE TESTING

See Section 5.1 for widening of test criteria in selected cases of cardiomyopathy and insulin resistance.

APPENDIX 3: EXAMPLE OF DATA RECORDS

The following are examples of participant descriptive data it is proposed will be collected. Added to this will be quantitative values of test measurements collected by function (cardiac, hepatic etc). While a set of core information will be defined at the outset, it is to be expected that experience will identify additional parameters which will be added. ALMS1 gene mutation data will also be stored.

Table for database of Alström UK participant demographic data

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<td>M/F</td>
<td>01/01/01</td>
<td>Drop down</td>
<td>Yes/no</td>
<td>Yes/no</td>
<td>Yes/no</td>
<td>01/01/01</td>
<td>01/01/01</td>
<td>5</td>
</tr>
</tbody>
</table>

Table for database of Alström UK participant anthropometric data

<table>
<thead>
<tr>
<th>date</th>
<th>BMI Kg/M2</th>
<th>Age at final height yrs</th>
<th>Blood pressure mmHG</th>
<th>therapy</th>
<th>Age when photophobic</th>
<th>Age visual impairment</th>
<th>Age registered blind</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>01/01/01</td>
<td>32</td>
<td>13</td>
<td>140/90</td>
<td>list</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table for database of Alström UK participant co-morbidities

<table>
<thead>
<tr>
<th>ID</th>
<th>Type 2 dm</th>
<th>Type 1 dm</th>
<th>No diabetes</th>
<th>Low HDL high triglyceride</th>
<th>Very high triglyceride &gt;5 mmol/l</th>
<th>Renal-CKD stage</th>
<th>Liver fibrosis</th>
<th>cardiac fibrosis</th>
<th>Skeletal problem</th>
<th>Date of first hearing problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes/no</td>
<td>Yes/no</td>
<td>Yes/no</td>
<td>Yes/no</td>
<td>Yes/no</td>
<td>4</td>
<td>Yes/no</td>
<td>Yes/no</td>
<td>Yes/no</td>
<td>Yes/no</td>
</tr>
</tbody>
</table>

### Table for Cardiometabolic data:

<table>
<thead>
<tr>
<th>Date</th>
<th>NYHA grade heart failure</th>
<th>NTPro BNP</th>
<th>% of normal Serum Creatinine micromol/l</th>
<th>BP Systolic mmHg</th>
<th>BP Diastolic mmHg</th>
<th>LV ejection fraction%</th>
<th>ECG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>