**OHIOH Type 1 Cohort: Advanced Eye Research Sub-study Protocol**

**Investigators & personnel (and their affiliations)**

Prof Christopher Nolan (Endocrinology, CHS; and ANU Medical School)

Prof Ted Maddess (Neuroscience, JCSMR, ANU)

Dr Maria Cecilia Garcia Rudaz (Paediatric Diabetes Clinic, CHS)

Dr Tony Lafferty (Paediatric Diabetes Clinic, CHS)

Dr Sally Newsome (Young Adult Diabetes Clinic, CHS)

Dr Robert Schmidli (Young Adult Diabetes Clinic, CHS)

A/Prof Rohan Essex (Ophthalmology, CHS; and ANU Medical School)

Prof Alicia Jenkins (NHMRC Clinical Trials Center, University of Sydney)

Dr Bhim Rai (Neuroscience, JCSMR, ANU)

Dr Faran Sabeti (Neuroscience, JCSMR, ANU)

Dr Corinne Carle (Neuroscience, JCSMR, and ANU Medical School, ANU)

Ms Emilie Rohan (Neuroscience, JCSMR, ANU)

Dr Josh Van Kleef (Mathematician, Neuroscience, JCSMR, ANU)

Ms Juliette Maenakaya (Orthoptist, Neuroscience, JCSMR, ANU)

Ms Karen Brown (Research Nurse, CHS)

Institution(s) responsible for the running of the study

ANU and Canberra Health Services

Contents

[1. Synopsis 2](#_Toc473989667)

[2. Abbreviations and Acronyms 3](#_Toc473989668)

[3. Introduction/Background 3](#_Toc473989669)

[*4.* Objectives 6](#_Toc473989670)

[5. Hypotheses 7](#_Toc473989671)

[6. Study Methodology 7](#_Toc473989672)

[7. Study population **Error! Bookmark not defined.**](#_Toc473989673)

[8. Study procedure 12](#_Toc473989674)

[9. Data Management 16](#_Toc473989675)

[10. Adverse Event Reporting 16](#_Toc473989676)

[11. Statistical Analysis 17](#_Toc473989677)

[12. Quality assurance, monitoring & safety 17](#_Toc473989678)

[13. Ethical Issues 18](#_Toc473989679)

[14. Finance and resource use 18](#_Toc473989680)

[15. Dissemination of Results and Publication policy 18](#_Toc473989681)

# Synopsis

This study is a sub-study involving participants of the Our Health in Our Hands (OHIOH) Type 1 Diabetes (T1D) Research Cohort. Participants who consent to be involved in this sub-study will have more comprehensive eye testing performed at the time of their annual diabetes complications screening visits, including testing with *multifocal pupillographic objective perimetry* (**mfPOP**) to determine its utility in assessing T1D participants for diabetes complications involving the eye and the nervous system.

The ANU Neuroscience team has developed the mfPOP method and have published several studies indicating that mfPOP is able to identify several levels of visual dysfunction before there are classical retinal vascular changes referred to as diabetic retinopathy (**DR**). Additionally, the group has published studies showing the ability of mfPOP to assess early stages of the somewhat related disease, age-related macular degeneration (**AMD**). In addition to assessing retinal function, mfPOP may also be a very sensitive method to assess diabetic neuropathy. Initially several hypotheses will be tested in a cross-sectional study of young patients with T1D. The study will be extended as a longitudinal study with a 5-year follow-up to assess change over time, and how this relates to diabetes control and to development and progression of diabetes complications. Prof Maddess, one of the ANU leads, has a strong track record of taking laboratory neural science into clinical practice and it is therefore likely that if useful information arises it will be brought into practice.

As the greatest benefit of mfPOP in diabetes in assessing diabetes complications is likely to be in the early stages of their development (e.g. before usual clinical tests for these conditions are positive), the young T1D participants of The OHIOH Type 1 Cohort (likely to have early rather than advanced complications) will provide an ideal group for this research.

# Abbreviations and Acronyms

List Abbreviations and Acronyms (as per the example below)

|  |  |
| --- | --- |
| AMD | Age-related Macular Degeneration |
| Anti-VEGF | Anti-Vascular Endothelial Growth Factor |
| AGE | Advanced Glycation End-product |
| ANU | Australian National University |
| BCVA | Best Corrected Visual Acuity |
| CHS | Canberra Health Services |
| DME | Diabetic Macular Edema |
| DR | Diabetic Retinopathy |
| eGFR | Estimated Glomerular Filtration Rate |
| ETDRS | Early Treatment Diabetic Retinopathy Study |
| HbA1c | Haemoglobin A1c |
| JCSMR | John Curtin School of Medical Research |
| mfPOP | Multifocal Pupillographic Objective Perimetry |
| OCT | Optical Coherence Tomography |
| OHIOH | Our Health in Our Hands |
| PIS | Participant Information Sheet |
| T1D | Type 1 Diabetes |

# Introduction/Background

Diabetic retinopathy is the leading cause of blindness among working age adults in the western world, and most patients with T1D will develop some form of diabetic eye disease within 20 years of diagnosis.(1) Perhaps more disturbing is that about 30% of T1D patients will develop potentially sight-threatening Diabetic Macular Edema (**DME**).(2, 3) Other complications include: heart disease and stroke, reduced kidney function (nephropathy) and kidney failure, blood vessel disease affecting the limbs (peripheral vascular disease) and nerve damage that typically involves the feet (peripheral neuropathy) that combined can lead to amputation, or damage to the nerves that regulate blood pressure, heart rhythm and gut function (autonomic neuropathy). The eyes provide a good site to monitor diabetic complications because they are damaged early in the disease, we can easily look inside the eyes, and the optic nerve has as many axons proceeding to the brain as the spine. Thus, effects of diabetes upon a substantial part of the nervous system can be monitored. An important aspect of this study is that T1D typically develops before young adulthood, so damage due to diabetes needs to be managed well; otherwise even with a low incidence of conversion to blindness or other serious complications, the accumulated lifetime risk is large.

The primary risk factor for diabetic complications is poor glycaemic control. If we had a tool (like mfPOP) that could reliably inform patients on the degree to which their sight and nervous system are at risk, this might help promote protective behaviours. Beyond that there are an increasing number of viable treatments for diabetic complications, particularly eye disease. For example the very large ACCORD(4) and FIELD(5) studies showed that fenofibrate reduced DME by 30%, reduced the severity of vascular DR, and other co-morbidities. Anti-VEGF injections into the eye and steroids have been shown to be quite effective in managing DME. The latter, however, are very much rescue therapies. Improved sensitive assessment methods for early diabetic eye disease will allow for the testing of new therapies (e.g. fenofibrate) at the earlier phases of the disease pathogenic processes.

The equipment for *multifocal pupillographic objective perimetry* (**mfPOP**) testing has received clearance from the US Food and Drug Administration (FDA). The mfPOP device has protocols for assessing both wide-field and macular visual field regions. As the name suggests the new device is objective and non-contact. The main mfPOP protocols (widefield or macular) objectively assess 44 visual field regions per eye at the same time, and in under 7 minutes. A new mfPOP screening-test protocol, with an 80-second test duration, is suitable for children. Our two published studies of early stage diabetic retinopathy,(6, 7) and two recently completed studies in participants with diabetes, all indicate that the mfPOP can measure localized visual field dysfunction in eyes in which the retinas show no vascular changes, and then several levels of increasing dysfunction in early stage non-proliferative disease. These functional lesions occur before any reported by standard automated perimetry.(8) The dysfunction quantified by mfPOP occurs well before any neuropathy of the iris, which in any case would masquerade as a global sensitivity change, not localized damage. These results are further supported by three published studies of early stage macular degeneration showing similar results.(9-11) We have shown that mfPOP can predict with some reliability which exudative AMD eyes will respond to anti-VEGF treatment.(12) Anti-VEGF treatment is increasingly used to treat DME. Finally, the localized visual field changes observed on mfPOP testing are also observed on testing patients with the more intrusive multifocal visual evoked potential (mfVEP) method.(13)

**Overall Aim**

To test young persons (age 8-22) with T1D with variants of the mfPOP test to assess their value in diabetes management.

In the first year, a cross-sectional study of patients aged 8 to 22 years who come through the pediatric and young adult diabetes clinics and are part of the OHIOH Type 1 Diabtetes Cohort at CHS will be assessed by mfPOP. Other standard eye tests will be done for correlative purposes. Aside from looking at correlations between age at onset and years of T1D and mfPOP findings, we will also examine acute changes in function around the time of initial diagnosis. We would then proceed to expand the cohort studied with plans to run a 5 year longitudinal study. The longitudinal study would specifically address issues of the power of mfPOP to predict outcomes like transition to non-proliferative and proliferative DR, as well as DME, or to the development of other complications such as peripheral neuropathy. In patients with DME, we will compare mfPOP function corresponding to the site of the DME and its surrounding retinal/visual field areas. The extent and position of DME would be determined by posterior pole optical coherence tomography (**OCT**) scans. We will also recruit putatively normal participants in order to obtain normative data for the mfPOP tests. Normative data has been obtained for three 7-minute mfPOP test methods for persons aged 18 to 79, but especially for the newer shorter screening-test, normative data is required, particularly in children and adolescents.

**References**

1. Klein BE. Overview of epidemiologic studies of diabetic retinopathy. Ophthalmic Epidemiol. 2007;14:179-83.

2. Klein BE, Myers CE, Howard KP, Klein R. Serum Lipids and Proliferative Diabetic Retinopathy and Macular Edema in Persons With Long-term Type 1 Diabetes Mellitus: The Wisconsin Epidemiologic Study of Diabetic Retinopathy. JAMA Ophthalmol. 2015;133(5):503-10.

3. Klein R, Klein BEK, Moss SE. Relation of smoking to the incidence of age-related maculopathy - The Beaver Dam Eye Study. American Journal of Epidemiology. 1998;147(2):103-10.

4. Accord Eye Study Group, Chew EY, Ambrosius WT, Davis MD, Danis RP, Gangaputra S, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med. 2010;363(3):233-44.

5. Herrmann M, Sullivan DR, Veillard AS, McCorquodale T, Straub IR, Scott R, et al. Serum 25-hydroxyvitamin D: a predictor of macrovascular and microvascular complications in patients with type 2 diabetes. Diabetes Care. 2015;38(3):521-8.

6. Bell A, James AC, Kolic M, Essex RW, Maddess T. Dichoptic multifocal pupillography reveals afferent visual field defects in early type 2 diabetes. Invest Ophthalmol Vis Sci. 2010;51(1):602-8.

7. Sabeti F, Nolan CJ, James AC, Jenkins A, Maddess T. Multifocal pupillography identifies changes in visual sensitivity according to severity of diabetic retinopathy in type 2 diabetes. Invest Ophthalmol Vis Sci. 2015;56(8):4504-13.

8. Sabeti F, Mallikarjunan R, Nolan C, Corinne CF, Maddess T, James AC, editors. A comparative analysis of changes in visual field sensitivity in type 2 diabetes. ARVO - Invest Ophthalmol Vis Sci; 2015; Denver CO, USA.

9. Sabeti F, James AC, Essex RW, Maddess T. Multifocal pupillography identifies retinal dysfunction in early age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol. 2013;251(7):1707-16.

10. Sabeti F, Maddess T, Essex RW, James AC. Multifocal pupillographic assessment of age-related macular degeneration. Optom Vis Sci. 2011;88(12):1477-85.

11. Sabeti F, Maddess T, Essex RW, Saikal A, James AC, Carle CF. Multifocal pupillography in early age-related macular degeneration. Optom Vis Sci. 2014;91(8):904-15.

12. Sabeti F, Maddess T, Essex RW, James AC. Multifocal pupillography identifies ranibizumab-induced changes in retinal function for exudative age-related macular degeneration. Invest Ophthalmol Vis Sci. 2012;53(1):253-60.

13. Sabeti F, James AC, Essex RW, Maddess T. Dichoptic multifocal visual evoked potentials identify local retinal dysfunction in age-related macular degeneration. Doc Ophthalmol. 2013;126(2):125-36.

# Objectives

1. Complete a cross-sectional study of patients as a sub-study of the OHIOH Type 1 Diabetes Cohort, aged 8-22, with T1D and obtain normative data from age and sex-matched control participants. The study will examine the relationships between age of T1D onset, diabetes duration, the level of glycaemic control, blood lipid status and visual function as assessed by mfPOP; and to relate visual function as assessed by mfPOP to the presence of other diabetes complications including presence of DR and DME.
2. Commence enrollment of patients for a 5-year prospective study to examine visual function as assessed by mfPOP over time according to parameters of metabolic control and the development of clinically significant DR, DME and other diabetes related-complications.

**Impact**: The results may show mfPOP to be of use as a novel, rapid, and quantitative test for assessment of diabetes-related tissue injury, particularly eye complications. Furthermore, mfPOP readouts may be shown to be useful as surrogate end-points for progression of diabetes-related tissue injury in clinical trials focused on the prevention of diabetic complications.

# Hypotheses

1. mfPOP can be used as a screening and monitoring tool for diabetic retinopathy and diabetic macular edema.
2. mfPOP can be used as a screening and monitoring tool for diabetic neuropathy.
3. mfPOP can provide a clinically useful more general measure of diabetes-induced tissue injury.
4. mfPOP will provide a valuable tool for assessment of new therapies directed at the prevention of diabetes complications such as retinopathy and neuropathy.

# Study Methodology

**6.1 Study type and methods**

To achieve the study objectives with testing of all 4 hypotheses, the following studies will be performed.

**i) Cross-sectional study.**

In the first year participants with T1D aged between the ages of 8 and 22 years participating in the OHIOH Type 1 Diabetes Cohort will be recruited from the paediatric and young adult diabetes clinics at Canberra Health Services. All participants will have clinical data recorded and complications screening performed, as outlined in the OHIOH Type 1 Diabetes Cohort base-level protocol (see attachment). For this advanced eye research sub-study, additional eye tests will be performed, including mfPOP (see section 6.2). The panel of eye tests will vary according to the age of the participants; with more limited tests being performed in children (see section 6.2).

Control participants without diabetes will also be recruited to obtain normative data for comparison in the cross-sectional study.

One in three participants, 16 years and older, in the cross-sectional study will be invited to have repeat mfPOP testing 2 weeks after the initial test to assess reproducibility of the method.

**ii) Prospective study.**

Participants recruited to the cross-sectional study and the new onset diabetes studies will be invited to be followed-up annually for 5 years.

**6.2 Eye testing at baseline (and annually for subjects being followed prospectively).**

**6.2.1 Participants 16 years and older (OHIOH T1D Cohort participants)**

* Best Corrected Visual Acuity (**BCVA**) using the Early Treatment Diabetic Retinopathy Study (**ETDRS**) eye chart
* Stereo Fly and Randot tests of binocular depth perception
* N30-5 screening visual field test on a Matrix perimeter (one minute for each eye)
* Colour photographs of the retinal surface (5 photographs per eye as per ETDRS standard) taken by non-mydriatric camera
* Slit lamp examination and air-puff tonometry
* Posterior pole and optic nerve head OCT scans
* A macular mfPOP (7 minute) test, and two 80 second tests: wide-field (w20) and a macular (m18) test of both eyes at the same time will be performed. Finger prick blood glucose will be performed immediately before mfPOP testing. The 7 min test will be performed first
* For the first assessment, one in three participants will be invited to undergo repeat mfPOP testing 2 weeks later (including with a finger prick blood glucose level) to determine reproducibility of the method

**6.2.2 Participants 8-15 years of age (OHIOH T1D Cohort participants)**

The array of vision tests will be reduced to lessen burden of testing:

* BCVA (ETDRS eye chart)
* Stereo Fly and Randot tests of binocular depth perception
* Colour photographs of the retinal surface (2 photographs per eye as per Australian screening standards) taken by non-mydriatric camera
* Posterior pole and optic nerve head OCT scans
* The two 80 second tests: wide-field (w20) and a macular (m18) test of both eyes at the same time will be performed. Finger prick blood glucose will be performed immediately before mfPOP testing
* If the 80 sec mfPOP tests are well tolerated, the child participants will be invited to undertake the 7-minute macular mfPOP test

**6.2.3 Control participants**

As control participants are not part of the base-level OHIOH T1D cohort, they will not have had recording of clinical information and assessments that the T1D advanced eye research substudy participants will have had through their base-level involvement. For this reason, in addition to completing the eye testing protocol (as described in 6.2.1 and 6.2.2), control participants in the advanced eye research substudy will also require collection of clinical data (including stage of puberty assessment), as well as the assessments as occurs in the annual OHIOH T1D Cohort base-level complications screen (see below). They will also have the finger stick blood glucose measurement immediately before mfPOP. 1 in 3 control participants will be asked to attend for mfPOP retesting 2 weeks after the initial test to determine reproducibility.

**6.2.3.1 Clinical information and assessments of control subjects (as occurs for T1D in their base-level OHIOH participation)**

• Record medical history details - first visit.

* Refresh background history details subsequent visits (e.g. development of comorbid conditions, new family history).

• Weight, height, body mass index, waist circumference.

• Lying and standing systolic/diastolic blood pressure using a manual blood pressure recorder with appropriate sized cuffs– mean of 2nd and 3rd of 3 readings (note: pulse wave pressure will be calculated from the 2nd last 2 readings also (systolic – diastolic measurements).

• Arterial stiffness- pulse pressure analysis from blood pressure measurements.

• Neuropathy- biothesiometer threshold recording both feet (Bio-Medical Instrument Company, Newbury, Ohio, USA).

• Glycaemic tissue injury- skin advanced glycation end-product (AGE) assessment – (DiagnOptics skin test).

• Venous blood sample (first year and every third year) for HbA1c, renal function- urea, creatinine, estimated glomerular filtration rate (eGFR), fasting cholesterol, triglyceride, HDL cholesterol, LDL cholesterol (ACT Pathology).

• Thyroid function tests and a coeliac disease screen blood test will be performed every third year (ACT Pathology).

• Random urine sample for albumin/creatinine ratio every third year (ACT Pathology).

* Puberty status (clinically assessed or self-assessed until menarche in girls or until puberty in boys)

**6.4 Explanatory notes**

1. All T1D participants involved in the advanced eye research sub-study will already be participants of the base-level OHIOH Type 1 Diabetes Cohort and will have data recorded on their clinical history, examination findings and biochemical pathology testing, as indicated in the base-level OHIOH Type 1 Diabetes Cohort protocol.
2. The testing of participants less than 16 years will be less extensive (shorter mfPOP test and only 2 retinal photographs per eye), so as to reduce the potential discomfort of multiple tests.
3. For retinal photography, the current standard clinical practice is to take 2 images per eye. The 5-photo method is required to rate the severity of diabetic eye disease according to the international ETDRS standard. Hence, from the age of 16, 5 photographs per eye will be taken which is different from usual practice. Photo grading will be done independently by an independent professional reading-center and the results will be made available to the clinicians managing the participants.
4. OCT testing is not standard for screening for diabetic eye disease. However, OCT scans are a key part of the NHMRC’s 2008 best practice guidelines for management of diabetic retinopathy, particularly for detecting DME. DME is only poorly visible on retinal photography but is very well characterized by OCT. There is limited information on the presence of DME in young persons affected by T1D. OCT is non-invasive and is expected to be well tolerated by all age children.
5. The eye tests will be conducted by suitably qualified persons, trained in optometry, orthoptics or ophthalmology.
6. Blood testing for control participants will be funded by the study and performed every third year instead of yearly.

# Study Population

**7.1 How many participants?**

Cross-sectional and prospective follow-up studies

In the first year we expect to recruit up to 150 young T1D patients to the OHIOH T1D Cohort. Those within the cohort, from age 8 and above will be eligible for this Advanced Eye Research sub-study and will be invited to participate.

Control participants-

For our current mfPOP normative data-base, we have 6 males and 6 females within 5-yearly cohorts, the youngest age being 18 years. For this study, taking into account changes that occur with growth and onset of puberty, we will obtain data from 6 males and 6 females in each of the following cohorts according to age: giving the steps 8-9, 10-11, 12-13, 14-15, 16-18, 19-22 years of age. Thus, we will test about 72 control participants. Control participants will be recruited with assistance of the T1D participants who will be able to invite their friends.

**7.2 Inclusion/Exclusion criteria**

Inclusion criteria:

* Persons in the age range of 8-22 years at baseline with T1D and control participants without T1D
* English speaking (they will need to be able follow instructions for the various eye tests)
* Ability to perform the tests

Exclusion criteria

* T1D participants: any eye condition other than that caused by diabetes
* Control participants: any eye condition
* All: Medications that could affect iris or retinal function including systemic steroids and treatment for epilepsy. Patients with other significant co-morbidities

# Study procedures

**8.1 Patient informed consent process**

**Participants with T1D:** As for the consenting process for the base-level involvement in the OHIOH T1D Cohort, for this sub-study, there are different information and consent processes for participants who are minor persons and those who are adults (16 years and older). The primary difference is that in the case of minor participants consent is obtained from both the participant (assent) and their parent or guardian. Given that the Participant Information Sheet (**PIS**) for adults is a long document (Appendix 2 of main application), we rely on the parent or guardian to decipher and understand that. There is a separate Information for Minor Participants form (Appendix 3) that includes some age-appropriate subject information that is based upon the PIS. For children under 12, we anticipate that the document will be read to them by their parent or guardian and assent would be verbal and given in front of a project principal investigator or OHIOH Research Nurse. Older children who wish to sign the assent section of the consent form will be able to do this.

**Controls:** Separate PIS and consent/assent forms, as well as information sheets for Minor Participants will be provided as additional clinical information and assessments are required (as collected for base-level involvement in the OHIOH T1D Cohort) as per Section 6.2.3.1..

Participants of OHIOH Type 1 Diabetes Cohort eligible for this sub-study may volunteer (information will be available on the OHIOH website) or be invited by the OHIOH team. If they agree, the investigator will then provide the approved PIS, explain the study, and answer questions. They will be given the opportunity to take the forms home and discuss with family, their general practitioner or anyone else, or they can provide consent at that time. If they do wish to take the paperwork away to discuss or think about their potential participation, we will phone them (patient or parent/guardian) after 1 week once, to see if they are interested in participating. If after that call the person does not wish to participate, they will not to be contacted again for this particular sub-study. All participants (parents/guardians) agreeing to participate will need to sign consent forms (+/- assent) with signatures of the investigator and a copy of the PIS and signed consent form will be provided back to the signatories for their records. Informed consent will be similarly obtained from controls (patient or parent/guardian).

**8.2 Study visits and data collection**

For the OHIOH Type 1 Diabetes Cohort participants, the additional eye examinations required for this sub-study will be performed on an annual basis coinciding with the annual complications screening visits of their base-level involvement. An additional 30 min (making total time commitment of 1 h 30 min) will be required for these extra tests. For the control subjects, 60 min will be required for the first visit, then 40 min for each return visit.

**8. 3 Study outcomes**

1. The cross-sectional study will improve understanding of how mfPOP readouts relate to early-stage diabetic eye disease (DR and DME) as assessed by ETDRS fundal photographs and OCT assessment.
2. The cross-sectional study will improve understanding of how mfPOP readouts relate to the presence and severity of non-ocular diabetes complications, such as neuropathy (biothesiometer reading), (albumin excretion and eGFR) and non-specific tissue damage (AGE reading).
3. The cross-sectional study will improve understanding of the relationships between age of T1D onset, diabetes duration, the level of glycaemic control, BMI, blood lipid status and visual function as assessed by mfPOP.
4. Complete the mfPOP normative data base for young participants
5. Data on short-term reproducibility in controls and T1D patients, will also be obtained
6. The longer prospective study will mainly examine rates of transition to standard clinical end-points for diabetic tissue damage and the degree to which these can be predicted by mfPOP. The end-points would include the development of DME, non-proliferative DR, and proliferative DR, as well as markers of non-ocular diabetes complications.

**8.4 Further subject follow-up**, if applicable

Current funding for this sub-study is for 5 years only. It is hoped the study will continue beyond 5 years depending on outcomes of this study and ongoing funding.

**8.5 Study timelines**

Each study session requires about 1.5 hours, so about 5 participant-visits per day. Thus for 150 participants to complete the test sessions of the cross-sectional study of year 1, 80 test-days will be required, i.e. about 2 days per week. For the follow-up prospective study, assuming 100 participants participate, will require about one testing day per week in the subsequent 4 years.

**8.6 Patient withdrawal**

* Participants may stop testing within this OHIOH sub-study or all components of the OHIOH study at any time. If they request, we will delete their data from the study.
* Participants would be withdrawn by the investigators if they develop an exclusion criterion or fail to comply with the study procedures.

**8.7 Risk / benefit**

The risk to participants is extremely low relative to the testing they would normally do as T1D patients. The mfPOP device is extremely safe and has FDA clearance based on it being a Class 1 non-contact device. To date over 15,000 mfPOP tests have been done with no adverse events. By contrast, the possible benefits to future patients with diabetes in terms of new tests that would assist with treatments and management is relatively high.

# Data Management

Central to the OHIOH project is optimising the use of participant data to enable precision care for individual participants. To achieve this, OHIOH needs a platform by which individual participant data can be combined with data from many participants to enable analysis through machine learning approaches, eventually leading to readouts that inform personalised precision care to the individual participant. The underlying principles to be followed are (i) protection of the individual participant’s data and identity, (ii) enhancing quality of data available within the individual’s medical record to enhance clinical care, (iii) to ensure optimal ethical use of combined data to facilitate the objectives of transforming the health care that can be provided to all participants. Built into the OHIOH project is research into optimal management of big data sets including ethical issues and data security issues. Processes to ensure security of data will be updated on a regular basis.

Several levels of data need to be considered.

**Clinical data used in usual patient care**

* Participants enrolled in the OHIOH T1D Cohort will be assigned a unique code, within a register or “look up database” kept separate from the OHIOH database, such that all data within the main OHIOH participant database is de-identified, but re-identifiable (see below this section, 5 & 6).
* Data generated by OHIOH required for usual patient care will be provided to the patient’s medical record. Data within the patient medical record will be held according to the ACT Health Records (Privacy & Access) Act 1997.
* The use of data within the patient medical record required for OHIOH research purposes (i.e., to be extracted from the usual medical record for research) will be as specified in the approved ethics protocols. Extracted data will be de-identified using the participant unique code as above, before it will be entered into the OHIOH participant database.

**Retrieval of data from the OHIOH database for research use**

* The data within the OHIOH participant database will be available to approved researchers for performing analyses according to research objectives of the overall project. Often this will not require reference back to the individual participants from whom the data were generated. At times, however, the analyses will generate research questions that will need the researchers to go back to the participants, such that re-identification of the participants will be required. This will occur via the manager of the register.

**Retrieval of individual participant reports from the OHIOH participant database – clinician use**

* To meet the objectives of the project of precision care for individual participants, it is expected that reports relevant to the care of individual participants and validated for clinical use will be generated by the OHIOH database and then be passed onto the individual participant’s treating clinicians and the participant’s medical record. A request will be made by the clinician with the participant’s consent to the manager of the register who will pass on a de-identified request for such reports to be generated from the OHIOH database.

**Data storage**

* Considering the large quantities of data expected, the OHIOH participant database will be stored with the National Computer Infrastructure (NCI) on the ANU campus. To ensure participant confidentiality, the data will be stored securely being password protected and only named team members will have access. The data will be stored indefinitely.

**Future Use of Cohort Data**

* It is expected that the data will progressively accumulate such that its use will allow enhanced capacity of machine learning approaches to produce clinically relevant readouts. Thus, the data will be held indefinitely and will be used repetitively for the objectives of the OHIOH research and to inform improvements in patient care beyond the project.

# Adverse Event Reporting

As the OHIOH T1D Cohort is performing observational research only, it is not expected that there will be any adverse events or serious adverse events other than potential bruising/discomfort from blood draws.

As specified in the PIS, if participants have any concerns or problems regarding their participation in this project, they are asked to contact the Principal Investigators listed on the PIS. Additionally, participants are invited to contact the ACT Health and/or ANU HRECs and are provided with the contact details of both Committees.

# Statistical Analysis

Since there are effects of multiple measurements at several levels: visual field regions, eyes, pupils within participants, and multiple visits which will occur at different ages and stages of puberty, we will look at effects of disease variables using linear mixed-effects models. To examine differential rates of conversion to various end-points, e.g. onset of DME, onset of proliferative DR, we will use Kaplan-Meier survival analysis. Diagnostic power will be examined using cross-validated Receiver Operator Characteristic (**ROC**) analysis.

**Sample size**

We will attempt to enroll 150 participants with T1D into the cross-sectional study in the first year. Recruitment into subsequent years may be required if a cohort of 150 participants is slower than expected. The aim (dependent on funding) is to extend the recruitment phase to 5 years with the target of retaining participants within the study for 5 years. Based on data from our recent study of 23 T1D participants and 25 controls and using the mean mfPOP response delays per participants, we can calculate powers for mfPOP to different T1D participants from control participants according to the presence of no visible DR, mild DR and moderate non-proliferative DR. For p=0.05 a sample size of 100 provides powers for the three groups of: 0.84 for very mild risk, 0.90 for mild risk, and 0.99 for moderate risk. Thus even for half the participants that we plan to test there appears to be adequate power to detect functional changes in eyes with no classical DR or DME.

#  Quality assurance, monitoring & safety

This project will be monitored by the Clinical Director of Endocrinology and Clinical Director of Paediatrics at The Canberra Hospital and the Management Committee of OHIOH. The OHIOH Health Experience Advisory Board will have the opportunity to review protocols and will be regularly updated on progress of the project. They will be able to recommend revision of protocols and procedures if issues of concern arise.

There are no interventions within the study. No changes to any existing interventions, e.g. insulin treatment, will be made based upon any mfPOP data. Oversight of the mfPOP testing will be by Prof Ted Maddess and of the clinical testing will be overseen by Prof Christopher Nolan. The mfPOP device itself has several levels of quality assurance built into it including continuous regulation of the test light levels, continuous monitoring of signal quality, and quantification of the proportion of the test intervals without blinks or fixation losses. All this information, and live video of the test participant’s eyes are presented to the operator.

Any problems or concerns presented by participants will be reviewed by the project researchers and the Health Experience Advisory Board, and if required by the relevant HREC.

# Ethical Issues

**Consent**

The participants will be invited to participate by the OHIOH Type 1 Diabetes Cohort team. As described in Section 8 above consent will be obtained before the testing begins. These documents make it clear that the tests are not a treatment for diabetes, and participation or non-participation in the testing will have no effect on participant care. The participants are able to stop testing at any time.

The Regulatory Compliance and Clinical Practice standards are minimized by the lack of interventions. The persons dealing with the participants will complete Good Clinical Practice certificates.

As indicated in the OHIOH Research Project Framework document, all human research within OHIOH will be conducted in accordance National Statement on Ethical Conduct in Human Research 2007 (Updated 2018) and will require approval of the ACT Health HREC. All ACTH HREC approvals relating to this project will be shared with the ANU HREC.

**If unexpected clinical abnormalities are detected**

If the results of standard clinical assessments (e.g. standard eye tests) show clinically significant abnormalities, these results will be passed on to the participant’s general practitioner and specialist endocrinologist for them to further investigate and manage.

# Finance and resource use

This project is funded by the ANU. No investigator or member of research staff will receive a personal financial benefit from participant involvement in this project above usual salary. Direct costs include research team wages, purchase of questionnaires and assessment tools, training in the use of standardised measures and consumables for blood collection, analysis and storage. Indirect costs include participant transport. All costs will be funded by the ANU Grand Challenges scheme.

# Dissemination of Results and Publication policy

Outcomes from this project may be presented at scientific conferences, such as national and international diabetes conferences, published in medical journals and made available on the ANU Our Health in Our Hands program website (<http://www.anu.edu.au/research/research-initiatives/our-health-in-our-hands>). Copies of journal articles will be available from the lead researchers upon request. In any publication, information will be provided in such a way that individual participants cannot be identified.