

Australian Autism Biobank follow-up cohort pilot study

FINAL REPORT

Professor Valsamma Eapen Dr Anne Masi

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Australian Government Department of Industry, Science, Energy and Resources Business Cooperative Research Centres Program

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Final Report

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The Cooperative Research Centre for Living with Autism (Autism CRC)

The Cooperative Research Centre for Living with Autism (Autism CRC) is the world's first national, cooperative research effort focused on autism. Taking a whole-of-life approach to autism focusing on diagnosis, education and adult life, Autism CRC researchers are working with end-users to provide evidence-based outcomes which can be translated into practical solutions for governments, service providers, education and health professionals, families and people on the autism spectrum.

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A note on terminology

We recognise that when referring to individuals on the autism spectrum, there is no one term that suits all people. In our published material and other work, when speaking of adults we use the terms 'autistic person', 'person on the autism spectrum' or 'person on the spectrum'. The term 'autistic person' uses identity first language, which reflects the belief that being autistic is a core part of a person's identity. Autism Spectrum Disorder (ASD) is diagnostic terminology used by the healthcare sector, and is used in the context of a person being 'diagnosed with Autism Spectrum Disorder'.

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1. Introduction

1.1. Background

The aim of the Australian Autism Biobank ('Biobank') was to create a large Australian repository of phenotypic and biological information of young autistic individuals and their parents that can be used to facilitate earlier and more accurate diagnosis of autism and increase knowledge of the autism spectrum and co-occurring conditions.

Funding for the recruitment phase of the Biobank finished on 30 June 2018. The original Biobank study design had a recruitment target of 1,200 children on the autism spectrum across four sites (NSW, Queensland, Victoria, Western Australia). The original Biobank study design did not include samples from siblings (without an autism diagnosis) and age-matched controls. The Biobank study design was subsequently amended to include samples from non-autistic siblings and age-matched controls. The Biobank study recruited 929 children on the autism spectrum (probands). In addition, phenotype data and biological samples were included in total numbers for 239 probands from the WA Autism Biological Registry (WAABR) following reconsent and an approval for a waiver of consent. The Biobank also received samples from parents, siblings and controls. Final recruitment numbers were considered very successful and are represented in Table 1.

Table 1: Australian Autism Biobank Recruitment

	NSW	QLD	VIC	WA	Total
Probands (including ASD-Q)	289	198	201	480	1,168
Mothers	193	132	136	126	587
Fathers	117	91	84	104	396
Siblings (non- autistic)	54	86	42	80	262
Controls	22	19	21	88	150
Total Participants	675	526	484	878	2,563

Final recruitment numbers

Expanding the size of the Biobank cohort would allow data collection for Australian children on the spectrum to continue. This would facilitate capturing trends in diagnostic shifts (eg gender, ethnicity, socioeconomic status etc) and support work into understanding potential biological and

phenotypic subgroups across the autism spectrum utilising a larger dataset. However, baseline data represents a snapshot in time of an individual's phenotype, clinical characteristics and biospecimens. A second time point, or 'longitudinal follow-up' of the Biobank cohort, would provide vital information about the clinical characteristics and behavioural and genetic factors that may have an impact on children on the spectrum and their developmental trajectory. It would also provide important information on predictors of outcomes for children on the spectrum including valuable information about their cognitive, behavioural, social and communication characteristics. Knowledge of developmental trajectories could also provide insights into the type of future supports and needs required by those on the spectrum. The addition of a second set of biological samples, would allow for the stability of a biomarker through development over time to be investigated.

To determine whether a longitudinal follow-up of the Biobank cohort was feasible, a 6-month pilot study was proposed to investigate recontact and return rates for the original Biobank participants. The 6-month pilot was planned to operate at one site only (NSW). The recruitment target was 65 children on the spectrum to complete follow-up appointments over a 6-month period. Samples were to be processed and frozen on site, then transported in batches (see Figure 1) to the NSW Health Statewide Biobank (NSWHSB) for storage and quality control. As the aims of the study are to determine recontact and return rates for Biobank participants who consent to be recontacted, it was proposed that only core measures were to be administered and questionnaires collected, and blood and/or saliva collected. Additional samples such as urine, stool and hair were not included. Collection of pilot eye-tracking data was also included in the protocol to determine the feasibility of including an assessment of neurocognitive function in a longitudinal follow-up study.



Figure 1. Longitudinal follow-up timeline

A Biobank follow-up cohort pilot study will add value to the previously created Australian Autism Biobank asset for the Autism CRC that will be highly sort after by researchers from around the world. The Australian Autism Biobank has drawn attention from both research and industry. Data on the feasibility of a longitudinal follow-up would be useful for both the large-scale grant applications required for the continuation of the project outside Autism CRC funding and to attract industry investment.

1.2. Aims

- 1. Determine the return rate for follow-up study:
 - a) Determine rates of previous participants who consent to recontact;
 - b) Ascertain percentage of study population who consent to be recontacted who are able to be located;
 - c) Determine percentage of study population who can be contacted who consent to participate in follow-up.
- 2. Obtain follow-up data on consenting participants for blood and/or saliva, questionnaires and face-to-face assessments, and pilot data for eye-tracking.
- 3. Comparison of sample quality obtained from Australian Autism Biobank (transport prior to processing) and samples processed on site.

2. Research design and methods

2.1. Ethics

An ethics amendment was submitted to The Sydney Children's Hospital Network (SCHN) HREC (HREC Reference: HREC/14/SCH/269). SCHN HREC approval was obtained on 9th October 2018 (Appendix A). Research Governance approval was received on 23rd October 2018 from The Children's Hospital at Westmead and Sydney Children's Hospital Randwick Research Governance Office (Appendix A). Negotiations with the NSW Health Statewide Biobank (NSWHSB) to collect and accept samples for processing was undertaken.

The longitudinal follow-up was incorporated into the original ethics protocol for the Australian Autism Biobank study (HREC/14/SCH/269) and was presented as a feasibility or pilot study ("sub-study"). SCHN HREC requested additional information, clarification and modifications on two occasions prior to approving the longitudinal follow-up amendment. Clarification of the rationale for undertaking the "sub-study" was requested to be provided with reference to The National Statement on Ethical Conduct in Human Research (N.S) 2007, section 1.1(a). It was noted that an additional aim of the follow-up component was to characterise developmental trajectories in children on the autism spectrum. SCHN HREC also requested justification of the sample size. It was explained that the

sample size for the feasibility study was based on levels of recruitment of probands previously achieved for the Australian Autism Biobank project. It was further explained that over the course of the Biobank study, the average number of participants recruited in a month at the NSW site was 10, and therefore, it was anticipated that the proposed sample size after 6 months of recruitment will be approximately 60 children on the autism spectrum. An additional modification that was requested by SCHN HREC included a telephone script to be used when following up families via phone and an invitation email that could be sent to families (N.S.2.2.9). (Appendix A).

SCHN HREC were concerned about the scope of genetic testing and analysis to be conducted as part of the "sub-study" (Reference: The National Statement on Ethical Conduct in Human Research (N.S) 2007 (Updated 2018) section 1.1(b)). It was clarified that the blood and/or saliva sample will be analysed for gene specific DNA methylation changes and the stability of biomarkers will be tested by comparison with analysis undertaken on samples collected at the participant's first visit.

2.2. Study recruitment

The longitudinal follow-up operated as a pilot in one state only (NSW), to determine the feasibility for a longitudinal follow-up across the four sites from the first phase of the Australian Autism Biobank (NSW, Queensland, Victoria, Western Australia). Families of children on the spectrum who participated in the Australian Autism Biobank study could indicate an interest in being contacted about future studies. Firstly, they could tick a box ('yes' or 'no') on the consent form (Appendix A) in response to the statement:

• I would like to be contacted in the future about participating in further follow-up studies

Secondly, they could respond to a question in the Family History Questionnaire (FHQ) which was completed by the parents or caregivers of all children recruited to the Biobank (Appendix B). The FHQ included a question asking families if they would be interested in being contacted about future research:

• K.1 Would your family be happy to receive invitations to take part in further studies?

Families indicating they would be happy to receive invitations to take part in further studies or would like to be contacted in the future about participating in further follow-up studies were contacted via phone, email or post and asked whether they might be interested in participating in the 'Biobank Follow-up Sub-Study' using scripts (phone or email) approved by SCHN HREC (Appendix A). Parents or caregivers were contacted if there was at least 10 months between participation in the Biobank and the longitudinal follow-up. Interested participants were then provided with the 'Australian Autism Biobank Follow-up' Participant Information Sheet and Consent Form (Appendix A).

Based on previous rates of recruitment, a subgroup of approximately 60 participants from the original cohort of children on the spectrum were expected to return for repeat clinical and behavioural (cognitive and functional) assessments and questionnaires to track developmental progress. A blood and/or saliva sample was also requested.

2.3. Study methods

Assessments for the 'Australian Autism Biobank follow-up cohort study' (AAB-FUS) in NSW were conducted at the Child Development Unit, The Children's Hospital at Westmead, SCHN. The Child Development Unit provides comprehensive multidisciplinary care to children with complex developmental problems. Prior to attending the Child Development Unit, The Children's Hospital at Westmead, SCHN for assessments, families were asked to complete the following standardised published questionnaires:

- a. Vineland Adaptive Behaviour Scales (Sparrow et al., 2005)
- b. Tanner stages (Marshall & Tanner., 1969, 1970)
- c. Short Sensory Profile-2 (Dunn, 2014)
- d. Social Responsiveness Scale-2 (Frazier et al., 2014)

The Social Responsiveness Scale-2, which measures the social ability of children within the autism spectrum and was previously approved for sibling and control cohorts in the Biobank study was included as a screen. During the visit to the Child Development Unit (approximately 1.5 hours) data was collected on communicative and social behaviours relevant to the diagnosis of autism, an assessment of cognitive ability was completed, as well as anthropometric measurements including head circumference, height and weight. Tanner stages were collected and recorded when applicable. The following measures were administered:

- e. Autism Diagnostic Observation Scale (Lord et al., 2001)
- f. Mullen Scales of Early Learning behaviours relevant to the diagnosis of autism (Mullen, 1995) or
- g. Wechsler Scales of Intelligence (Wechsler, 2003)

A blood and/or saliva sample was requested from each participant enrolled in the study. The blood and/or saliva sample will be analysed for Gene specific DNA methylation changes and the stability

of biomarkers will be tested by comparison with analysis undertaken on samples collected at the participants first visit. An Assessment Checklist (Appendix B) was completed for each participant.

Study data were collected and managed using REDCap electronic data capture tools (Harris et al., 2009; Harris et al., 2019). The REDCap project was initially hosted at UNSW, Sydney. A project was created in REDCap titled 'Biobank Follow-up Study' data. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources. Hard copies of assessments and questionnaires were scanned, checked for legibility and uploaded to the 'Biobank Follow-up Study' on REDCap. The Australian Autism Biobank: Data Entry Manual (Version 5, 12.07.2018) was referenced for all data entry related tasks. The hard copies of assessments and questionnaires will be archived with the hard copies from the Australian Autism Biobank study.

3. Findings

Of the 289 children (aged 2-17) recruited by the NSW site to the Biobank, 190 were recruited through the Child Development Unit, The Children's Hospital at Westmead, SCHN. The Family History Questionnaire (FHQ: K.1 – Appendix B) or the consent form (Appendix A) for these participants was reviewed to identify whether the family had agreed to be contacted about further studies. The workflow relating to determining the return rate for the AAB-FUS is shown in Figure 2.



Figure 2. Workflow implemented to determine the return rate for follow-up study

*A+B: Families who agreed to be recontacted about future or follow-up studies **F: Number of participants who can be contacted who consent to participate in follow-up AAB; Australian Autism Biobank. CDU; Child Development Unit, The Children's Hospital at Westmead.

Table 2: Recruitment numbers for the AAB-FUS

	N	% Total Biobank recruitment from CDU	% Total consent for recontact	% Total recontacted
Number of participants recruited through CDU, Westmead	190			
Number of families who agreed to be recontacted (FHQ or consent form)	176	93%		
Number of children aged 2-17 years at time of recruitment for AAB-FUS	171	90%		
Number who were not followed up as time between assessment for Biobank and AAB-FUS study < 12 months	15			
Number of participants (aged 2-17) who consent to be recontacted who are able to be contacted	108	57%	69%	
Number of participants (aged 2-17) who could NOT be recontacted	48	25%	31%	
Number of participants who can be contacted who consent to participate in follow-up	63	33%	40%	58%
Average age of participants in AAB-FUS (range)	7.1 (2.9 – 17.1)			

AAB-FUS; Australian Autism Biobank follow-up cohort pilot study. CDU; Child Development Unit, The Children's Hospital Westmead, Sydney Children's Hospital Network. FHQ; Family History Questionnaire.

The percentage of participants in the Australian Autism Biobank who were recruited through the Child Development Unit, The Children's Hospital at Westmead, SCHN, NSW and consented to be recontacted about future studies was 93%. The percentage of the study population who were eligible for follow-up (ie. aged 2-17, > 12 months between first assessment and follow-up assessment) and who consented to be recontacted and were able to be located and contacted was 69%. The percentage of the eligible study population who were contacted and who consented to participate in follow-up was 58%.

Data for the AAB-FUS was obtained using face-to-face assessments and questionnaires completed by parents or caregivers (Table 3). Eye tracking pilot data was obtained for a subgroup of participants. Assessment appointments were conducted from December 12^{th} , 2018 to 15^{th} April 2019 (approximately 16 weeks). Families preference was to attend assessments during school holidays, with 68% (*N* = 43) of face-to-face assessments conducted during NSW school holidays. Face-to-face appointments averaged approximately 5 per week during school holiday periods. Families were provided with a report summarising the results of the assessments (Appendix C).

Table 2: Assessments completed and questionnaires returned

Assessment	N completed
ADOS-2	62
SRS-2	60
MSEL	27
WISC-IV	32
VABS-II	59
SSP-2	61
Tanner Stages	14
Clinical Proforma	61
Saliva	58
Eye Tracking Tasks	24

Abbreviations: ADOS-2; Autism Diagnostic Observation Scale, 2nd Edition. MSEL; Mullen Scales of Early Learning. SSP-2; Short Sensory Profile–2. SRS-2; Social Responsiveness Scale, 2nd Edition. VABS-II; Vineland Adaptive Behaviour Scales, 2nd Edition. WISC-IV; Wechsler Scales of Intelligence, 4th edition.

The first aim of the study ie. to determine the return rate for the follow-up study, was achieved seamlessly and efficiently. For the second aim of the study, the confirmation of diagnosis assessment (ie. ADOS-2) was successfully conducted on 62 children whilst the cognitive assessment was administered for 59 children. Administration of the ADOS-2 and WISC could not be completed for one child due to behaviour. The WISC was not appropriate for two other children who did could not complete tasks. Mullen couldn't be completed for one child as he was not focused or tired. Return rates on parent completed questionnaires was excellent in the context of the demands on parent's time and the time taken to complete these questionnaires (approximately 60 minutes).

Sample collection:

A saliva sample was obtained from the majority of participants. Saliva collection was not possible for five children who did not allow the collection to occur. The parents were given the saliva collection kit to take home to attempt collection, but the parents were unable to successfully collect the amount of saliva required. Collecting saliva from this cohort is difficult so collection from all but five participants can be considered a good outcome.

The majority of parent/carers would not consider the child providing a blood sample. In the final sample only saliva samples were provided. During the first phase of this study ie. the Australian Autism Biobank Study, participating families recruited through the Child Development Unit, The

Children's Hospital at Westmead, were generally undertaking a blood draw for clinical purposes. The blood sample for the Biobank was obtained at the same time the child was undergoing the blood draw for clinical purposes. However, the majority of parent/carers were not interested in consenting for a blood draw for the AAB-FUS as there was not a clinical reason for the child to provide a blood sample.

Eye tracking:

The eye-tracking assessments were undertaken in conjunction with another project based at the Child Development Unit, The Children's Hospital at Westmead, SCHN where ethics approval for eye-tracking tasks had already been obtained. SCHN HREC advised that the addition of the eye-tracking task to the original Australian Autism Biobank ethics (HREC/14/SCH/269) would not be possible without a new ethics application being submitted. Given the timelines this was not an option.

Consent forms were signed for both the AAB-FUS study (incorporated within HREC Reference: HREC/14/SCH/269) and the 'Predictors of Early Intervention for Autism' study (HREC Reference: HREC/16/SCHN/47). Recruitment to the 'Predictors of Early Intervention for Autism' study was approved for children aged from 2 to 7. There were 44 children recruited to the AAB-FUS who were within this age range. Eye-tracking assessments were successfully completed for 24 children participating in the AAB-FUS. The proportion of eligible children who completed the eye tracking tasks was 55%. The tasks were attempted with other children, but the child would either not sit and attend to the tasks, or if they were sitting, they had difficulty attending to the task, so the amount of data collected was inadequate for analysis. Some parents decided their child could not participate in the eye tracking tasks due to the time that the ADOS-2 and Mullen assessments had taken, or they thought that their child would not be able to sit and watch the screen for five minutes.

4. Limitations

The participants who had agreed to be followed up were easily identifiable due to the question asked about follow-up studies in the FHQ (Q K1) and the inclusion of a question regarding participation in future studies and tick box in the consent form. However, as expected, there were a number of contact attempts required to eventually communicate with families and inform them about the AAB-FUS. The attempts to contact families were logged and the process was time consuming. There was a concern about attempting to contact families on too many occasions, so attempts to contact were limited to four attempts.

The generalisation of findings may be difficult due to a potential bias in who agreed to participate in the follow-up assessments. Families were provided with a brief report following assessments (Appendix C). It is possible that those who were wanting a report for National Disability Insurance Scheme (NDIS) purposes may have been highly motivated to participate leading to a possible bias.

It is clear that parents/carers were not interested in their child providing a blood sample without a clinical purpose. Therefore, it will be challenging obtaining blood samples for analysis from this population in any future studies unless there is a clinical reason for the child to provide a blood sample. Providing other biological samples are unlikely to prove as challenging given the high proportion of saliva samples obtained.

The New South Wales Health Statewide Biobank (NSWHSB) provided pricing for sample collection, processing (extraction of DNA) and storage. There were significant delays in obtaining the pricing, service agreement and materials transfer agreement from the NSWHSB. This may have been a function of the low number of samples involved in this study and therefore it was a low priority for NSWHSB. It was not possible to obtain collection and quality control processing as detailed in Figure 1. This was due to the low number of samples and the relatively high costs to undertake this work for a small number of samples at multiple timepoints.

5. Implications for research and practice

It remains a challenge to achieve high return rates for a face-to-face follow-up study if the follow-up is not aligned with a clinical service (e.g. follow-up at start of school or for an assessment that would result in a report for NDIS or other purposes). Families are highly motivated to obtain reports for the purpose of an NDIS planning or plan review meeting and hence future planning for a follow-up study should consider NDIS plan and review report requirements.

6.Key Recommendations

- It is recommended that a "research" follow-up should be combined with a clinical face-toface attendance for a clinical reason or purpose, in order to increase participation and completion rates.
- 2. It is also recommended that all questionnaires are completed online prior to attendance to reduce appointment time and data entry related tasks.
- 3. Eye tracking tasks should be administered on portable devices to improve uptake and quality of data collection.

- 4. Families should be provided with the option to attend the nearest pathology lab for a biological sample collection. It is possible that arrangements can be put in place for blood draws to occur in the home. This may improve the proportion of participants agreeing to provide a blood sample. In addition, samples collected at sites throughout NSW can be transported to NSWHSB directly using the option available for free collection of samples across the state. It may be possible to negotiate with NSWHSB to transport samples from other states to NSWHSB.
- It is highly recommended that negotiations with NSWHSB (or equivalent state services) take place at study conception and design phase to ensure features such as quality control are incorporated and priced to ensure budgetary allowances are made.

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Appendix A

Biobank Follow-up Sub-Study: SCHN HREC approval

Ç	The Sydney children's Hospitals N	etwork		
	care, advocacy, resear	ch, education		
	Contact for ti Research Eth Research Eth Phone: (Facsimile: (Email: <u>S</u>	his corresponder ics Office ics Administration 02) 9845 1253 02) 9845 1317 SCHN-ethics@hea	nce: Assistant a <u>lth.nsw.gov.au</u>	Corner Hawkesbury Road and Hainsworth Street Locked Bag 4001 Westmead NSW 2145 Sydney Australia DX 8213 Parramatta Tel +61 2 9845 0000 Fax +61 2 9845 3489 <u>http://www.schn.health.nsw.gov.au/</u> ABN 53 188 579 090
	9 October 201	18		
	Professor Val Mental Health Academic Uni Liverpool Hos	samma Eapen Centre it of Child Psychiat pital	try	
	Dear Prof Eap	ben		
	HREC Refere	ence:	HREC/14/SCHN/269	
	Project title:		The Australian Autism Biobank	
	Site/s:		The Children's Hospital at West Ingham Institute for Applied Me Campbelltown Hospital	mead dical Research, SWSLHD
	I acknowledge	e receipt of your pr	roject amendment submitted 25 Jul	y 2018, requesting approval for:

1. This amendment relates to a subgroup of approximately 60 participants

from the original cohort of 288 probands returning for repeat clinical and behavioural (cognitive and functional) assessments to track developmental progress. A blood and/or saliva sample will also be obtained.

The amendment/s was reviewed at the meeting of the Executive Committee of the Sydney Children's Hospitals Network Human Research Ethics Committee (SCHN HREC) at its meeting held on 2 August 2018 and the response to the request for further information on the 13 September 2018 and subsequently by the Executive of SCHN HREC on the 8 October 2018.

I am pleased to advise that the documents reviewed and approved at the meeting were:

Documents Reviewed	Version	Date
Amendment form		18 Jul 2018
Participant consent form	V1	24 Jul 2018
Cover letter		27 Aug 2018
Questionnaire Pages from SRS_2_PreSchool		Received 27 Aug 2018
Questionnaire Pages from SRS_2_SchoolAge		Received 27 Aug 2018
Cover letter		27 Sep 2018

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Participant information sheet	V4	04 Oct 2018
Study protocol	V16	27 Sep 2018
Telephone & Email Script	V2	Received 27 Sep 2018

This lead HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Research Involving Humans* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

This letter constitutes ethics amendment approval ONLY. A copy of this letter must be forwarded to the Research Governance Officer at each site for governance approval.

This application has been assessed in accordance with, and meets the requirements of the National Statement on Ethical Conduct in Human Research (2007).

Should you require any further information, please do not hesitate to contact the Research Ethics Office at <u>SCHN-ethics@health.nsw.gov.au</u> or on (02) 9845 1253.

Yours sincerely,

Sarah Garnett

Associate Professor Sarah Garnett Chair, Sydney Children's Hospitals Network Human Research Ethics Committee Sydney Children's Hospitals Network Human Research Ethics Committee cc Anne Masi

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Biobank Follow-up Sub-Study: SCHN Research Governance Authorisation



The Children's Hospital at Westmead and Sydney Children's Hospital Randwick Research Governance AMENDMENT FORM

 The proposed amendment must not be implemented at a SCHN site until you have received:

 (i) Lead HREC approval for this amendment and

 (ii) Research Governance approval (which is a signed copy of this form by RGO)

 Guideline
 link:

http://www.schn.health.nsw.gov.au/research/research_governance.php

		Yes	No	RG OFFICE	
				use	
				ONLY	
Project title	The Australian Autism Biobank			\boxtimes	
Principal investigator	Professor Valsamma Eapen			Comment [GB1]: Note to Researcher:
	Dr. Natalie Silove			this should b Coordinating also the PLa	e the PI at the Site. Not the PI (CPI) unless the CPI is t the site
Date submitted	12/10/2018				
HREC reference number	HREC/14/SCHN/269				
HREC amendment number (if					
applicable)					
Have you received Lead HREC		Yes	No	⊠-	
approval for this amendment?		\boxtimes		noted	
(HREC amendment and approval <u>must</u> be				HREC	
attached! Please note, this will not be				approva	
provided to governance by SCHN				Lietter	
HREC!) (Optional: list all HREC approved				Tietter	
documents)				on	
				90ct18	
SSA approval number	SSA/14/SCHN/437			\boxtimes	
Site	SCH (Randwick) PNES				
	CHW (Westmead) 🛛 🛛 Bear Cottage 🗌	1			
	NETS Children's Court				
Please advise actual start date of	1/1/2015				
project at this site					
Brief amendment description	1. Amendment to Study Protocol and New			\square	
	Participant Information Sheet and Consent				
	Form. This amendment relates to a subgroup				

						-		_
		of approxi	mately 60 pa	articipants	from the			
		original cohort of 288 probands returning for						
		repeat clinical and behavioural (cognitive and						
		functional) assessmen	ts to track				
		developm	ental progre	ss. A bloo	d and/or			
		saliva sam	pie will also	be obtain	ed.			
		Study protoc	ol V16	27 Se	0 2018			
List any	site specific documents	Doc	ument	Version	Date	Yes	No	\boxtimes
which <u>re</u>	equire amendment	Participant	Consent	1	24 July 2018	\square		
(Please at	tach tracked and clean version)	Form	consent	-	21741/2020			
		Participant	Information	4	4 October			
		Sheet			2018			
Are you	changing study					Yes	No	\bowtie
personn	el? (Study personnel includes:						\boxtimes	
investigat	ors & other study staff)							
You mus	st provide evidence of	If YES	, attach			Yes	No	⊠-
support	from the Department	Declaration B attached:			\boxtimes		Sandra	
Head of	the department	(http://www.schn.health.nsw.gov.au/research/research					Pengilly-	
responsi	ible for the project	_governance.php)					12.10.1	
acknowl	edging this amendment						8	
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		governance.php)						
Does the	e amendment involve a	CTN				Yes	No	
change	to anything which affects						\boxtimes	
the initia	al governance approval?	Research agreement/ Indemnity/ CTRA			Yes	No		
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		Insurance coverage			Yes	No		
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Biobank Follow-up Sub-Study: Participant Information Statement







Participant Information Sheet - Parent/Guardian

The Australian Autism Biobank Follow Up

Professor Valsamma Eapen

What does participation involve?

This is an invitation for the child in your care, who has previously participated in the Australian Autism Biobank, to take part in this research project looking at differences in outcomes for children with autism spectrum disorders (ASD).

This Participant Information Sheet tells you about the research project. It explains the tests and research involved. Knowing what is involved will help you decide if you want the child to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not the child can take part, you might want to talk about it with a relative, friend or local doctor.

Participation in this research is voluntary. If you do not wish for the child to take part, they do not have to. There are no consequences to choosing not to participate. Participation will not have an impact on yours or the child in your care, relationship with the Child Development Unit at Westmead Children's Hospital or any of the other organisations involved in the research. They will receive the best possible care whether or not they take part.

If you decide you want the child to take part in the research project, you will be asked to sign a consent form. By signing the consent form you are telling us that you:

Understand what you have read in this Participant Information Sheet

- Consent to your child taking part in the research project
- Consent to your child having the tests and research that are described
- · Consent to the use of your child's personal and health information as described.

You will be given a copy of this Participant Information Sheet to keep.

Investiaators:

Professor Valsamma Eapen, Chair of Infant, Child, and Adolescent Psychiatry, University of New South Wales and Sydney South West Area Health Service and Dr Natalie Silove, Child Development Unit, Westmead

What is the purpose of this research?

Children with autism show different responses to intervention and varying trajectories over time. It is important to understand which underlying factors are able to predict better outcomes so that intervention can be tailored to suit each individual child. This research project aims to investigate

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Page 1 of 3

some of the clinical and babayiay cal factors that may have an impact on children with autism and their development over time. It will provide important information on predictors of outcomes for children with autism and also provide valuable information about cognitive, behaviay cal, social and communication characteristics of children with autism. The research project also aims to assess the stability of biomarkers such as gene specific DNA methylation and any changes over time. Understanding a person's genes also may be able to explain why some people respond to a treatment, while others do not.

Who can participate in the study?

Families of children with autism aged 2 to 17 who have previously participated in the Australian Autism Biobank, and have agreed to be recontacted about future research, are being asked to participate in this study. Families are being approached in NSW. Taking part in this study will not cost you anything.

What will parents and children be asked to do?

If you decide to take part, there will be three parts to your participation in the study.

- You will be asked to complete questionnaires about your child. These questionnaires will be sent to you before your scheduled clinical assessment, so they can be completed at home and you can bring the completed questionnaires when you and your child come to the clinical assessment. The questionnaires include information about child development, medical history, adaptive behaviour and autism symptoms. These questionnaires will take approximately 1 hour to complete. Only the researcher will have access to the scores after you complete these questionnaires.
- Your child / children will also be invited to attend a clinical assessment. In this session, your child with autism will take part in various child friendly games and activities. We will also take measurements of your child's face, arms and legs. This session has been designed to be fun for children.
- 3. A blood and/or saliva sample will be collected from children in the study. The blood sample of 12ml (approximately two teaspoons) will be collected from a vein in your child's arm. This can be distressing for some children. However, a local anaesthetic may be used to numb the area. If you or your child would like to stop this procedure at any time you may do so.

In all cases, information entered into computer files will not contain names or any other identifying aspects in order to maintain confidentiality and anonymity. Publications of results, in reports or papers, will not identify individual children or families. The data we collect from you and your child are published along with our scholarly articles. Importantly, we will never share any of your personal identifying information.

Are there any side-effects and risk associated with this study?

Some discomfort may be experienced when a blood sample is taken. A local anaesthetic cream can be applied to minimise pain. Afterwards a small bruise at the site of the blood collection may develop. There may also be slight discomfort when a saliva sample is taken.

What are the possible benefits in taking part?

The information we get from this study could help design better ways of assessing and helping future generations of people with autism.

What will happen to the participant's test samples?

As soon as you enter the study, your child and your family would be identified by a code number. The document matching your code numbers and names will be kept separately from the study data. The information we collect from the questionnaires and the clinical assessment will be entered into a secure electronic database. The hard copies of this information would be kept in a locked filing cabinet.

The biological samples we collect will be labelled with a code number, processed and stored in a locked freezer at a secure facility. The genetics of autism is complex, and these studies often take many years. We will retain all data collected for this study (including genetic information) indefinitely, with annual reviews.

What happens when the research project ends?

We plan to publish our findings in scientific journals. You can get general news about the studies at www.autismcrc.com.au.

Parents will also be provided with a brief report about their child. Should this study cause distress for you or your child please call the Karitane 24 hour telephone parenting information and counselling service on 1300 227 464.

What will happen to information about the participant?

By signing the consent form you consent to the relevant research staff collecting and using personal information about the participant for the research project. Any information obtained in connection with this research project that can identify the participant will remain confidential. The participant's information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about the participant may be obtained from their health records held at this and other health services, for the purpose of this research. By signing the consent form you agree to the research team accessing health records if they are relevant to participation in this research project.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that the participant cannot be identified.

Is there any other important information?

Participation in this project is voluntary and if you decide not to take part or decide to withdraw at any time this will not otherwise affect your child's care. If you do withdraw consent during the research project, the researchers will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly. You should be aware that data collected by the researcher up to the time a participant withdraws will form part of the research project results. If you do not want them to do this, you must tell them before the participant joins the research project. We would like to store the blood and/or saliva sample as part of the Australian Autism Biobank for use in any future research studies. Banking involves storing health information and biological samples for future research studies. A biobank is the place where the information is stored. The data collected as part of the Australian Autism Biobank will be stored as individually non-identifiable specimens. In the future, other researchers will be able to apply to access the Biobank in order to learn about the causes of autism.

If you would like any further information about this study, please do not hesitate to discuss them with Professor Valsa Eapen, Chief Investigator (9616 4364) or Feroza Khan on 0491 137 235. If you are interested in being involved in the study please complete the Participant Consent Form and return it to Feroza Khan via email <u>f.khan@unsw.edu.au</u> or post to University of New South Wales Level 1, 30 Botany St, Randwick NSW 2052.

This project has been approved by the Sydney Children's Hospitals Network Human Research Ethics Committee. If you have any concerns about the conduct of this study, please contact the Executive Officer of that Committee on (02) 9845 3066 or via email - <u>SCHN-Ethics@health.nsw.gov.au</u>

> Thank you for taking the time to consider this study. If you wish to take part in it, please sign the consent form. This information sheet is for you to keep.

Biobank Follow-up Sub-Study: Consent form







The Sydney children's

Participant Consent (parent/guardian and child) *The Australian Autism Biobank Follow-up*

Declaration by Parent/Guardian

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to the child participating in this research project as described and understand that I am free to withdraw them at any time during the project without affecting their future health care.

I understand that I will be given a signed copy of this document to keep.

Please indicate your consent for the following components of the study for your child / children:

Yes 🗌	No 🗌
Yes 🗌	No 🗌
Yes 🗌	No 🗌
	Yes 🗌 Yes 🗌

I consent to my child / children's samples being used for autism gene discovery, other biochemical research, and for research projects deemed appropriate after consideration by "The Australian Autism Biobank" Biobank Access Committee. I understand that the sample will not be used for purposes other than this. I also understand that the samples may be shared with other researchers for these purposes (and only these purposes), provided that names or addresses are not used.

I understand that through participation in this study, personal and sensitive information (including health information, and possibly information regarding ethnic or racial origin) will be collected, stored (indefinitely) and used as I would reasonably expect in accordance with The Australian Autism Biobank information sheet provided. This includes to record my child's participation, to undertake research related to autism (within and possibly outside Australia), process results and, if necessary, to contact me. I understand that I have a right to access any personal information held about my child (including to ensure its accuracy), or to complain about the handling of personal information, and that to do so I can contact any listed individual or institution on the information sheet provided.

I agree that research data gathered from the results of this study may be published and shared with other researchers, provided that names and addresses are not used.

Parent / Guardian Consent

Name of parent / guardian (please print):							
Signature of parent / guardian:							
Name of child / children (please print):							
Date:	Email:						
Address:							
Phone:		_Mobile:					

Name of child / children (please print)	Signature of child / children	Date

Biobank Follow-up Sub-Study:

Telephone Script

Hello, my name is I am a researcher from the University of New South Wales who has been working on the Australian Autism Biobank project.

As your child and family previously participated in the Australian Autism Biobank, and agreed to be contacted about future research, we would like to ask whether you wish to take part in a follow-up research project.

This would involve a follow-up assessment by a Research Officer from the University of New South Wales. The Research Officer would do a cognitive and autism assessment similar to the Australian Autism Biobank assessments and give you a report. You will also be asked to fill in questionnaires about your child which can be sent prior to the assessment. These assessments and questionnaires will help us to understand how children with autism progress over a period of time.

And, as well as the clinical assessment we will ask to obtain a blood or saliva sample from your child (approximately two teaspoons). The blood sample will be collected by trained and qualified staff. We can provide some resources to help prepare your child for a blood test.

Participation is voluntary.

Can we email you further information about the study?

(If parents' response is yes): Thank you for your interest. Can I please have your email address? I will send you the information and call in a week to see if you have any questions.

(If parents' response is no): Thank you for your time today. We appreciate your previous participation in the project.

Invitation Email

Dear,

We are running a research project with Dr Natalie Silove from the Child Development Unit at The Children's Hospital at Westmead and Professor Valsa Eapen from the University of New South Wales – *The Australian Autism Biobank*.

As your child and family previously participated in the Australian Autism Biobank, and agreed to be contacted about future research, we would like to enquire as to whether you wish to take part in a follow-up research project. The assessments and questionnaires that we will ask you and the child in your care to complete will help us to understand how children with autism progress over a period of time. Please note participation is voluntary.

Please find attached the participant information sheet for the project. I will call you next week to follow-up and answer any questions you might have, or please call me when it is convenient for you (p.)

This project has been approved by the Sydney Children's Hospitals Network Human Research Ethics Committee. If you have any concerns about the conduct of this study, please contact the Executive Officer of that Committee on (02) 9845 3066 or via email - <u>SCHN-Ethics@health.nsw.gov.au</u>

Many thanks for your interest in our project.

Yours sincerely,

Appendix B

Family history questionnaire Section K: Future contact

Section K: Future contact

K.1 Would your family be happy to receive invitations to take part in further studies?

□ No (go to Question K.3)

Yes 2

K.2 It would be helpful to us if you nominate two relatives or close friends who do not live with you who could advise use of a current address in the event that we lose contact with you.

Contact 1	Contact 2	
Name	 Name	
Address	 Address	
Phone number	 Phone number	



Please write below any comments concerning this questionnaire, the research, or anything else you would like to tell us about.

THANK YOU

We greatly appreciate the time that you have spent completing this questionnaire.

Thank you for contributing to autism research.

Biobank Follow-up Sub-Study:

Assessment Checklist

ID

Child Date of Birth: _____ /____/

Consent obtained:

🗖 yes

From Parents		Measure Collected:	Date completed: (DD/MM/YYYY)
Vineland Adaptive B	ehaviour Scales	□Yes □No □N/A	//20
Short Sensory Profile	3	□Yes □No □N/A	//20
SRS-2		🛛 Yes 🗖 No 🗖 N/A	//20
Notes:			
From Proband		Measure Collected:	Date completed: (DD/MM/YYYY)
ADOS-2 Module co	mpleted: 1 / 2 / 3 / 4 (please circle)	□yes □no □n/A	//20
		□Yes □No □N/A	//20
Tanner Stages (8+ years)		□Yes □No □N/A	/20
Clinical Proforma		□yes □no □n/A	//20
Notes:			
Biological Samples	s Sample collection details Date of sampl		Date of sample collection: (DD/MM/YYYY)
Proband	□Yes □No □N/A	Blood Saliva	/20

Appendix C

The Australian Autism Biobank - Follow-up Study

SUMMARY OF ASSESSMENT RESULTS

Name:	<name< th=""><th>></th></name<>	>
Date of birth:	<dob></dob>	
Date of assessment:	<date></date>	
Date of report:	<date></date>	
Name of parent/caregiver at assessment:	<names< td=""><td>s></td></names<>	s>

The Australian Autism Biobank Follow-up Study is a research study collecting detailed biological, behavioural, and cognitive profiles of children with autism and their parents who have previously participated in the Australian Autism Biobank Study. This study is being funded by the Autism Cooperative Research centre (<u>www.autismcrc.com.au</u>), which is a national research program aimed to improve the lives of people with autism and their families.

<insert name here> and their parent/caregiver <insert name here> completed a number of clinical assessments as part of this study. Below is a summary of the findings from each assessment. Please note these scores were collected for research purposes <u>only</u> and do not represent a comprehensive child developmental assessment.

Cognitive Abilities

Wechsler Intelligence Scale for Children-IV

The Wechsler Intelligence Scale for Children (WISC-IV) assesses general cognitive functioning in children aged 6 to 16 years. It consists of 10 separate subtests that measures both verbal skills and specific non-verbal skills. There are four measures of ability relating to verbal comprehension skills, perceptual organisation, working memory capacity, processing speed, and overall ability.

Index	Percentile	Description
Verbal Comprehension Index		
Perceptual Reasoning Index		
Working Memory Index		
Processing Speed Index		
Full scale IQ		

Table 1. Summary of scores on the WISC-IV

Note: 45th percentile indicates that performance was better than 45% of same age peers

<mark>OR</mark>

Mullen Scales of Early Learning

The Mullen Scales of Early Learning (MSEL) assesses cognitive ability and motor development in young children. The MSEL consists of five subscales evaluating gross and fine motor skills, visual reception, expressive language, and receptive language.

Table 1. Summary of scores on the Mullen Scales of Early Learning

Subscale	Percentile	Age equivalent (months)
Gross motor		
Fine Motor		
Visual Reception		
Expressive Language		
Receptive Language		

Note: 45th percentile indicates that performance was better than 45% of same age peers

Adaptive Behaviour

Vineland Adaptive Behaviour Scale-II (VABS-II)

The VABS-II is completed by parents or caregivers to obtain observations of their child's adaptive behaviours in the areas of communication, daily living skills, socialisation, and motor skills (in children under 6 years of age).

Table 2. Summary of scores on the VABS

Subdomain	Percentile	Adaptive level
Communication		
Daily living skills		
Socialisation		
Motor skills		
Adaptive behaviour composite		

Note: 45th percentile indicates that performance was better than 45% of same age peers

Diagnostic Assessments

Autism Diagnostic Observation Schedule (ADOS-2)

The ADOS-2 is a play-based diagnostic assessment of communication, social interaction, play, and restricted and repetitive behaviours.

Table 3. Summary of scores on the ADOS-2

ADOS-2 classification	
ADOS-2 comparison score	

Summary of findings

 $\frac{X}{X}$ presented as a <u>VERY BRIEF</u> <u>DESCRIPTION OF PARTICIPANT</u>. He/she displayed cognitive ability in the $\frac{X}{X}$ range and adaptive behaviour in the X range. Scores on the ADOS-2 confirmed classifications of $\frac{X}{X}$ and $\frac{X}{X}$.

This summary was generated based on data collected for <u>research purposes</u> and does not represent a comprehensive child developmental assessment.

For any further information, contact <site contact> on <phone> or <email>

Appendix D

Acknowledgements - Australian Autism Biobank

Children on the autism spectrum, their siblings and parents and other children who generously contributed their time and data/samples for the Australian Autism Biobank.

The various sites who supported recruitment for the Biobank:





Telethon Kids Institute Andrew Whitehouse Alexis Harun Dominique Cleary Jodie Leslie Anna Hunt Kendra Dommisse Claire Hafekost Anneliese Hopkins Brooke Peden Gail Alvares

UNSW

Valsamma Eapen Anne Masi Feroza Khan Nisha Mathew









La Trobe University Cheryl Dissanayake Lauren Lawson Rachel Jellett Melanie Muniandy Maryam Haghiran Grace Christou Erin Beattie

Mater Medical Research Institute Paul A Dawson Helen Heussler Helen Holdsworth Mira Frenk Michaela Nothard Melissa Neylan Dora Abbondanza Ola Rajapakse Mridu Radhakrishnan Institute for Molecular Biosciences, University of Queensland Jacob Gratten Naomi Wray Anjali Henders Leanne Wallace Jolene Berry Vandhana Bharti

Wesley Medical Research Emma Raymond Deborah Lennon Melanie De Jong

Autism CRC Felicity Rose



Autism CRC

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@autismcrc

Our values



Inclusion

Working together with those with the lived experience of autism in all we do



Innovation

New solutions for long term challenges



Independence

Guided by evidence based research, integrity and peer review



Cooperation

Bringing benefits to our partners; capturing opportunities they cannot capture alone



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