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Our reference 35073

16 April 2021

Associate Professor Dennis Lau
Medical Specialties

Dear Associate Professor Lau

ETHICS APPROVAL No: H-2021-053
PROJECT TITLE: Postural orthostatic tachycardia syndrome (POTS) in Long COVID syndrome: A detailed profiling study (POTS-LCS)

The ethics application for the above project has been reviewed by the Human Research Ethics Committee and is deemed to meet the requirements of the *National Statement on Ethical Conduct in Human Research 2007 (Updated 2018)*.

You are authorised to commence your research on: 16/04/2021
The ethics expiry date for this project is: 30/04/2024

NAMED INVESTIGATORS:

Chief Investigator:	Associate Professor Dennis Lau
Student - Postgraduate Doctorate by Research (PhD):	Mrs Marie-Claire Seeley
Student - Undergraduate Bachelors Honours:	Miss Erin Maelisa Welford
Associate Investigator:	Ms Celine Gallagher
Associate Investigator:	Dr Adrian Elliott
Associate Investigator:	Dr Tilenka Thynne

CONDITIONS OF APPROVAL: Thank you for addressing the feedback. The revised ethics application provided on the 15th of April 2021 has been approved.

Ethics approval is granted for three years and is subject to satisfactory annual reporting. The form titled Annual Report on Project Status is to be used when reporting annual progress and project completion and can be downloaded at http://www.adelaide.edu.au/research-services/oreci/human/reporting/. Prior to expiry, ethics approval may be extended for a further period.

Participants in the study are to be given a copy of the information sheet and the signed consent form to retain. It is also a condition of approval that you immediately report anything which might warrant review of ethical approval including:

- serious or unexpected adverse effects on participants,
- previously unforeseen events which might affect continued ethical acceptability of the project,
- proposed changes to the protocol or project investigators; and
- the project is discontinued before the expected date of completion.

Yours sincerely,

Professor Paul Delfabbro
Convenor

The University of Adelaide

THE UNIVERSITY of ADELAIDE

Human Research Ethics Committee (HREC)

2019 Application for ethics approval

Office use only	Received:					
	RM No.					
	Ethics Approval No:			H-2021-053		
	HREC	EXEC	A/P	HSc	Psych	ORECI

LEVEL OF ETHICAL REVIEW:

Indicate the level of ethical review that is being sought for this application:

☒	**Full HREC review** Applies to all research involving more than 'low risk research' as defined in the National Statement on Ethical Conduct in Human Research 2007 (updated 2018)
	Low risk review Applies to 'low risk research' as defined in the National Statement on Ethical Conduct in Human Research 2007 (updated 2018) (referred to hereafter as *National Statement)*. Research timetables should allow for the possibility that a project submitted as a low risk application may be deemed to involve more than low risk, or to raise other issues, therefore requiring full review. Researchers may be requested to provide additional information.

SECTION 1: PROJECT AND RESEARCHERS' DETAILS

1.1 Project title:

Postural orthostatic tachycardia syndrome (POTS) in Long COVID syndrome: A detailed profiling study (POTS-LCS)

1.2 Provide a 1-2 sentence plain language summary of the project:

This summary should be in plain language and suitable for release to the public.

This study aims to define the prevalence of postural orthostatic tachycardia syndrome (POTS) amongst patients with chronic illness post SARS-CoV-2 (COVID-19) infection – also known as Long COVID syndrome (LCS). Critically, this study also aims to unwrap the features of POTS amongst this cohort by looking at the contribution of inflammation, and autoimmunity towards chronic illness. The study will look at clinical biomarkers that may give an understanding of why the virus causes protracted and chronic illness in some people. Understanding of the viral onset of POTS may help guide targeted treatments for both LCS and the associated POTS.

1.3 Project timeframe:

Proposed commencement date of activities that require human ethics approval:	March 2021	**Estimated completion date of the project:**	March 2025

Research must not commence without the prior written approval of the HREC. Retrospective approval cannot be provided.

1.4 If this application is to extend a currently approved project, provide the HREC approval number:

HREC approval number:	H-2021-053

An Annual Report on Project Status Form should also be completed.

1.5 Applicant:

The applicant may also be referred to as the principal investigator. If the project is to be undertaken by a research student, the student's primary or other supervisor at The University of Adelaide is the Applicant.

Applicant's title and name:	Dr Dennis Lau	**EMPLID**:	a1149721
School or Department:	The University of Adelaide Centre for Heart Rhythm Disorders, (CHRD)		
Email:	dennis.lau@adelaide.edu.au	**Phone:**	08 8362 2273
Qualifications and research experience relevant to the project:	Dr Lau is a mid-career researcher and an opinion leader in heart rhythm disorders internationally. His research work has provided novel insights regarding catheter ablation of atrial fibrillation from mapping studies in both animal models and human subjects. He is also an active researcher on postural tachycardia syndrome, with a goal to improve understanding and management of this complex disorder. Recent publications from this work are being incorporated into international practice guidelines. He is a clinician scientist, appointed as a Research Fellow at The Centre for Heart Rhythm Disorders, University of Adelaide, and Cardiac Electrophysiologist at The Royal Adelaide Hospital, Adelaide, South Australia.		
Role in the research:	Principal Investigator		

1.6 Student projects:

If the project is to be undertaken by a research student as part of their studies, please indicate below. **Section 7** must also be completed.

Name:	Marie-Claire Seeley		A1288733	**Program Level:**	PhD
Name:	Erin Welford		A1720832	**Program Level:**	Honours

1.7 Other researchers:

List all researchers (other than the Applicant and students) in the table below and if applicable their University of Adelaide EMPLID. Include all co-supervisors and researchers internal and external to The University of Adelaide. **Section 7** must also be completed.

Names:	**EMPLID:**
Dr Celine Gallagher	a1662636
Dr Adrian Elliott	a1612710
Dr Tilenka Thynne	

1.8 Has or will this project be submitted for approval to other HRECs?

Include the HREC's name, current status of the application (i.e. submitted, approved, deferred or rejected) and attach this documentation. The University of Adelaide accepts ethics approval granted by some other HRECs and may not require a separate ethics application. Researchers are encouraged to consult with information about Notification of ethical review and approval from other institutions to see if this applies.

X No

1.9 Has or will this project be submitted for approval to any departments or institutions?

E.g. Department of Education, prisons, government institutions, or businesses. Attach authorising correspondence and/or approval documentation to the application.

☐ Yes – the project *will* be submitted for approval to:
☐ Yes – the project *has been* submitted for approval to:
☒ No

SECTION 2: NATURE OF THE PROJECT

2.1 Aims of the project:

Discuss in standard English the main research aims/hypotheses to be investigated.

The primary objective of this study is to:

[1] Assess the prevalence of POTS in those with LCS, using a standardised and detailed autonomic testing protocol

The secondary objectives of this study include:

[2] Characterising the neuroendocrine/inflammatory/immune biomarker profile of those with LCS(+)POTS/LCS(-)POTS and POTS and compare to matched, healthy controls

[3] Determining the impact of LCS with and without POTS and POTS on quality of life & symptom scores, cognitive function and psychological well-being and compare to matched, healthy controls

2.2 Rationale of the project:

Explain in standard English the rationale for the project i.e. how the research will fill any gaps or contribute new knowledge to the field.

The prevalence of POTS in sufferers of LCS is unknown, yet symptomatology of both syndromes share many commonalities. Quantifying the presence of POTS in those with LCS will provide significant insight to both the pathogenesis of POTS and the ongoing individual and global health impacts of COVID-19. The study has the potential to detail the incidence of POTS in 'long COVID' sufferers, thereby providing direction for diagnosis and treatment of this significant global cohort. Additionally, the study has the potential to provide understanding of disease pathophysiology in this post-viral syndrome. This will add to the aetiological understanding of the mechanisms of inflammatory and neuroendocrine disturbance in POTS. This work will help improve the diagnosis and management of the many LCS patients with dysautonomia.

2.3 Background to the project:

Briefly discuss any previous research of relevance and cite no more than 4 key references.

Long COVID Syndrome (LCS) is a term now frequently utilized to describe the collection of chronic symptoms lingering at ≥3 months post-acute SARS-CoV-2 infection.[1, 2] Several studies detail the presence of multi-systemic chronic symptoms such as fatigue, reduced cognition, exercise intolerance, pain and tachycardia in this cohort.[1, 2] While much remains unknown regarding LCS, involvement of the autonomic nervous system has been suggested.[3, 4]

The Office for National Statistics, UK have found that as many as 1 in 10 individuals are likely to suffer these symptoms post SARS-CoV-2 infection consistent with LCS.[5] With more than 108 million global cases of SARS-CoV-2 infection (as of February 13th 2021, Johns Hopkins Coronavirus Resource Center), there are potentially a high burden of LCS cases. Consequently, detailed characterization of this cohort of LCS patients is important as a high proportion of these individuals remain symptomatic with significant disability and unable to return to work.[6]

Postural orthostatic tachycardia syndrome (POTS) is a heterogenous disorder characterized by chronic and disabling symptomology that predominately affects young women of child bearing age.[7-9] POTS onset has a reported association with antecedent viral illness as well as concomitant autoimmune disease.[10, 11] Onset of this multisystemic disorder has been described in a recent case report after SARS-CoV-2 infection.[12] The pathophysiology remains unknown but may include post-viral autoimmunity, increased central sympathetic outflows, deconditioning/hypovolemia or neuro-endocrine related.[4] Indeed, inflammatory biomarkers and

adrenergic and cholinergic antibodies have been reported in POTS and are of interest in the pathogenesis of post viral onset of this syndrome and the interplay with inflammatory pathways and neuroendocrine dysfunction.[13]

While urine frequency and nocturia are frequently reported in POTS, these symptoms have generally been attributed to dys-innervation of the bladder similar to that experienced in an overactive bladder.[14 15] There is little in the way of research to establish whether those with POTS are experiencing true polyuria (>50 ml/kg 24hrs) or whether they are experiencing frequency and urgency as a result of dys-innervation of autonomic control of the bladder. Anecdotally, some with Long Covid describe a similar experience of periods of polyuria with associated cardiac symptomology. Establishing the underlying aetiology of polyuria and nocturia in these cohorts is crucial for identifying effective treatment options and important for improved understanding of contributing pathogeneses of LCS and POTS.

Previous animal models have demonstrated that increased renal bradykinin expression results in increased polyuria compensated by reflex polydipsia.[16] These studies also echoed the paradoxical finding of reduced plasma renin in the presence of established hypovolaemia previously noted in POTS cohorts.[17] The animals in these studies underwent several alterations to normal cardiovascular function similar to those characterised in POTS. Namely: excessively increased orthostatic heart rate, decreased heart rate variability, decreased LF/HF ratio and a paradoxically unchanged MAP and only slightly raised systolic BP.[16] This raises the consideration that inflammatory responses may play a role in disruption of the neuroendocrine feedback system that maintains fluid balance, resulting in hypovolaemia and cardiac augmentation. Additionally, others have reported elevated G-protein-coupled receptor antibodies in POTS cohorts and animal models and have demonstrated that presence of these autoantibodies' elicits symptoms of orthostatic intolerance, including cardiac augmentation. [18-23]

This study will provide insight into the interplay of inflammation, neuroendocrine function and dysautonomic control of heart rate and blood pressure that leads to the debilitating presence of POTS and/or LCS. Additionally, Delineating the prevalence of POTS in the LCS patients may help improve the diagnosis and management of this growing entity given the unprecedented global pandemic.

1. Huang C, Huang L, Wang Y, et al. 6-month consequences of covid-19 in patients discharged from hospital: A cohort study. *Lancet.* 2021;397:220-232. doi:10.1016/S0140-6736(20)32656-8

2. Mahase E. Covid-19: What do we know about "long covid"? *BMJ.* 2020;370:m2815. doi:10.1136/bmj.m2815

3. Dani M, Dirksen A, Taraborrelli P, et al. Autonomic dysfunction in 'long covid': Rationale, physiology and management strategies. *Clin Med (Lond).* 2021;21:e63-e67. doi:10.7861/clinmed.2020-0896

4. Goldstein DS. The possible association between covid-19 and postural tachycardia syndrome. *Heart Rhythm.* doi:10.1016/j.hrthm.2020.12.007

5. Caronavirus (covid-19) infection survey, uk: 5 february 2021. In: Statistics OfN, ed. UK: Office for National Statistics; 2021.

6. Davis HE, Assaf GS, McCorkell L, et al. Characterizing long covid in an international cohort: 7 months of symptoms and their impact. *medRxiv.* 2020:2020.2012.2024.20248802. doi:10.1101/2020.12.24.20248802

7. Goodman BP. Evaluation of postural tachycardia syndrome (pots). *Autonomic Neuroscience: Basic and Clinical.* 2018;215:12-19. doi:10.1016/j.autneu.2018.04.004

8. Shaw BH, Stiles LE, Bourne K, et al. The face of postural tachycardia syndrome – insights from a large cross-sectional online community-based survey. *Journal of Internal Medicine.* 2019;286:438-448. doi:10.1111/joim.12895

9. Zadourian A, Doherty TA, Swiatkiewicz I, Taub PR. Postural orthostatic tachycardia syndrome: Prevalence, pathophysiology, and management. *Drugs.* 2018;78:983-994. doi:10.1007/s40265-018-0931-5

10. Wells R, Elliott AD, Mahajan R, et al. Efficacy of therapies for postural tachycardia syndrome: A systematic review and meta-analysis. *Mayo Clinic Proceedings.* 2018;93:1043-1053. doi:10.1016/j.mayocp.2018.01.025

11. Lau DH, Mahajan R, Lee G, Kalman JM, Sanders P. Towards improved care of postural tachycardia syndrome, inappropriate sinus tachycardia and vasovagal syncope patients: A call to action in australia. *Heart, Lung & Circulation.* 2016;25:8-11. doi:10.1016/j.hlc.2015.10.001

12. Miglis MG, Prieto T, Shaik R, Muppidi S, Sinn DI, Jaradeh S. A case report of postural tachycardia syndrome after covid-19. *Clin Auton Res.* 2020;30:449-451. doi:10.1007/s10286-020-00727-9

13. Gunning WT, Stepkowski SM, Kramer PM, Karabin BL, Grubb BP. Inflammatory biomarkers in postural orthostatic tachycardia syndrome with elevated g-protein-coupled receptor autoantibodies. *Journal of Clinical Medicine.* 2021;10:623.

14. Kaufman MR, Chang-Kit L, Raj SR, et al. Overactive bladder and autonomic dysfunction: Lower urinary tract

symptoms in females with postural tachycardia syndrome. *Neurourol Urodyn.* 2017;36:610-613. doi:10.1002/nau.22971

15. Shoenfeld Y, Ryabkova VA, Scheibenbogen C, et al. Complex syndromes of chronic pain, fatigue and cognitive impairment linked to autoimmune dysautonomia and small fiber neuropathy. *Clinical Immunology.* 2020;214. doi:10.1016/j.clim.2020.108384

16. Barros CC, Schadock I, Sihn G, et al. Chronic overexpression of bradykinin in kidney causes polyuria and cardiac hypertrophy. *Front Med (Lausanne).* 2018;5:338-338. doi:10.3389/fmed.2018.00338

17. Raj SR, Biaggioni I, Yamhure PC, et al. Renin-aldosterone paradox and perturbed blood volume regulation underlying postural tachycardia syndrome. *Circulation.* 2005;111:1574-1582. doi:10.1161/01.CIR.0000160356.97313.5D

18. Abdallah H, Vo T, Alpan O. Autoantibodies, t, b and dendritic cell abnormalities in postural orthostatic tachycardia syndrome (pots). *Autonomic Neuroscience: Basic and Clinical.* 2015. doi:10.1016/j.autneu.2015.07.219

19. Hongliang L, Gege Z, Liping Z, et al. Adrenergic autoantibody-induced postural tachycardia syndrome in rabbits. *Journal of the American Heart Association.* 2019;8:1-9. doi:10.1161/JAHA.119.013006

20. Li J, Zhang Q, Liao Y, Zhang C, Hao H, Du J. The value of acetylcholine receptor antibody in children with postural tachycardia syndrome. *Pediatric cardiology.* 2015;36:165-170. doi:10.1007/s00246-014-0981-8

21. Loebel M, Grabowski P, Heidecke H, et al. Antibodies to β adrenergic and muscarinic cholinergic receptors in patients with chronic fatigue syndrome. *Brain, Behavior & Immunity.* 2016;52:32-39. doi:10.1016/j.bbi.2015.09.013

22. Xichun Y, Hongliang L, Murphy TA, et al. Angiotensin ii type 1 receptor autoantibodies in postural tachycardia syndrome. *Journal of the American Heart Association.* 2018;7:1-7. doi:10.1161/JAHA.117.008351

23. Kharraziha I, Axelsson J, Ricci F, et al. Serum activity against g protein-coupled receptors and severity of orthostatic symptoms in postural orthostatic tachycardia syndrome. *Journal of the American Heart Association.* 2020;9:e015989. doi:10.1161/JAHA.120.015989

24. Plash WB, Diedrich A, Biaggioni I, et al. Diagnosing postural tachycardia syndrome: Comparison of tilt testing compared with standing haemodynamics. *Clin Sci (Lond).* 2013;124:109-114. doi:10.1042/CS20120276

25. Van Batavia JP, Combs AJ, Fast AM, Glassberg KI. Overactive bladder (oab): A symptom in search of a disease - its relationship to specific lower urinary tract symptoms and conditions. *J Pediatr Urol.* 2017;13:277.e271-277.e274. doi:10.1016/j.jpurol.2017.02.010

2.4 Have there been any preliminary studies? If YES, provide the project title and HREC approval number(s):

Accompanying submission for Oz-POTS registry which will be drawn on for recruitment of POTS patients for this study.

2.5 Research methodology:

Describe how the study will be undertaken and explain what interactions will occur between researchers and participants. Include a description of the research methodology and how this will achieve the research aims. For example, you could include a justification of why the sample size/sampling method will yield valid and reliable results. Where appropriate, please refer back to the aims described in 2.1 when describing the methodological approach.

We plan to enrol 218 participants for this study (n= 150 with LCS, n=34 with POTS, n = 34 healthy matched controls). Subjects who meet the inclusion and none of the exclusion criteria and who provide informed consent, will be invited to attend in person to facilitate physical examination including autonomic testing, blood draw and associated investigations (see table below). The comprehensive nature of this exercise will allow subjects to complete various tools/questionnaires at their leisure via online portal links to a secure REDCap database, to reduce the impact of fatigue on the accuracy of findings.

Subject preparation:

48 hr before examination the following will be discontinued

- Anticholinergics
- Sympathomimetics (α and β agonists)
- Mineralcorticoids (Fludrocortisone)

24hr before examination the following will be discontinued

- Alcohol
- Salt tablets
- Caffeine
- Beta Blockers (propranolol, metoprolol), Ivabradine, Calcium channel blockers

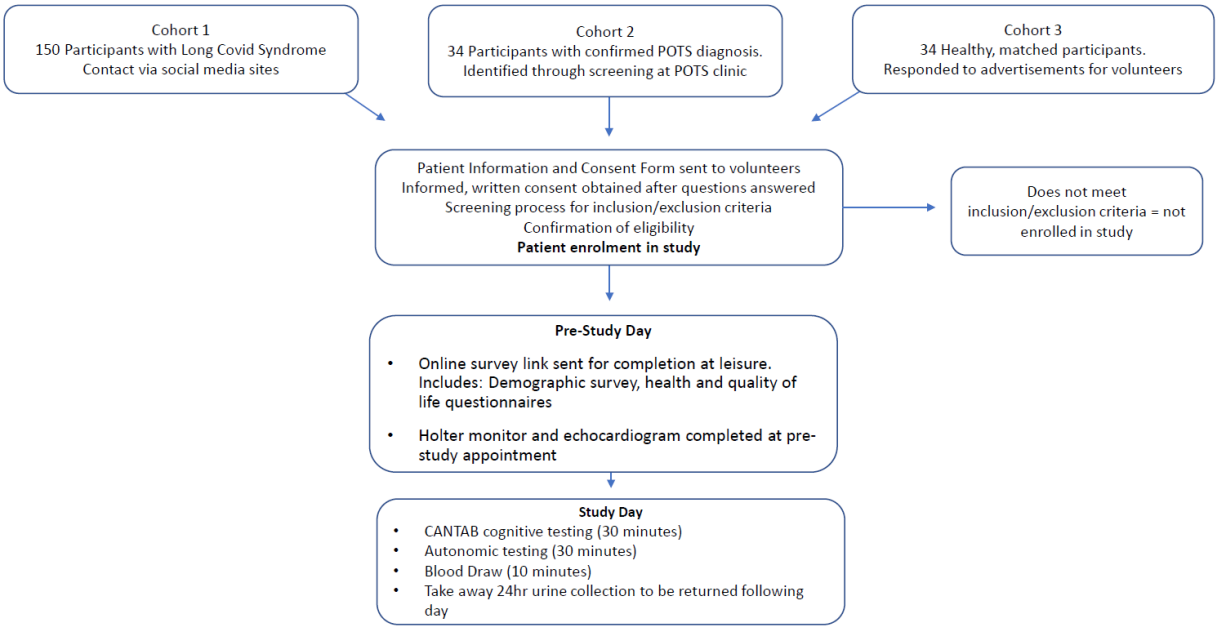
8 hrs before testing

- Fast from food
- Drink only water 'to thirst' and abstain from fluid 'loading'

On the morning of testing

- No wearing of compression wear
- No abdominal binders
- No support stockings

Figure 1: Project Schema



As participants in this study are excluded from having other significant cardiac impairments or significant medical conditions, it is unlikely that drug cessation will cause any detriment other than the discomfort and inconvenience of poorly controlled orthostatic intolerance. Participants will be encouraged to discuss cessation of medications with their regular doctor. In addition, senior clinician researchers will identify those in the screening process who may have increased risk if medications are ceased. If it is decided that individuals are unable to cease the above listed medications for the prescribed time, then those participants will not be able to participate in the study. This is the case because biomarker and autonomic testing outcomes would not be deemed meaningful in the setting of artificial control of heart rate and fluid status.

Study testing day:

The following testing protocol will take approximately 60-90 minutes to complete. A schematic representation of the protocol can be seen (Figure 1: above)
Non-invasive measurements of continuous arterial pressure and heart rate will be obtained using finger photoplethysmography (non-invasive blood pressure testing; NIBP) for 5 minutes before testing (rest) and then during each reflex test. This involves application of a small cuff to either of the 2nd to 5th digits of

one hand. The cuff is inflated to allow measurement of finger arterial blood pressure. This technique is well validated in a variety of clinical and experimental conditions and is similar to our prior protocol. Description of each test can be found in section 3.16

Testing variables	Cohort 1	Cohort 2	Cohort 3
Demographic Survey	X	X	X
Medical health history	X	X	X
Medications use	X	X	X
Physical examination	X	X	X
Health Related QoL			
- SF-36 [36-Item Short Form Survey]	X	X	X
- EQ-5D [5 level EQ score]	X	X	X
- COMPASS-31 [composite autonomic symptom scale]	X	X	X
- FSS [fatigue severity score]	X	X	X
- 5 Point hypermobility screen	X	X	X
- OHQ [orthostatic hypotension questionnaire]	X	X	X
Autonomic testing			
- Standing test, deep breathing, Valsava manoeuvre	X	X	X
- Sudomotor function (SUDOSCAN)	X	X	X
- 24-hour Holter monitoring	X	X	X
- Echocardiogram with Passive Leg Raise	X	X	X
Blood tests:			
-Complete Blood Panel and Electrolytes, CRP, ESR,	X	X	X
# TNF-α, IL-6, IL-1β, IL-10, IL-21, INFy, INF α/β, CD30,	X	X	X
# α1 adrenergic, Beta-1 adrenergic, M1 and M4 muscarinic cholinergic receptor Ab;	X	X	X
# Aldosterone, Potassium, Renin activity, copeptin level;	X	X	X
# Plasma Histamine, heparin, chromogranin A	X	X	X
24 hr Urinary volume and osmolarity	X	X	X
Cognitive and psychological testing			
- CANTAB (Cambridge neuropsychological test automated battery)	X	X	X
- HADS (hospital anxiety and depression scale)	X	X	X

2.6 Location(s) of the research:

Include details of all sites where the project will be undertaken and locations of participants.

Participant assessments will be undertaken by the Centre for Heart Rhythm Disorders (CHRD) at two sites. The first site is in Norwood, South Australia and the other Cardiovascular Services in Kew East, Melbourne, Victoria. Additionally, controls can undergo their autonomic testing in the clinical rooms at the UoA/SAHMRI, North Tce, Adelaide. This facility provides a clinical setting that is appropriate to the research and allows for added convenience for students who wish to volunteer for the research. No patients will be recruited from public health organisations and no data collection will take place at public health spaces. Due to the scarcity of specialists treating dysautonomia in Australia, many patients access care from interstate via telehealth or interstate visits to the Adelaide clinic. Use of private rooms in Melbourne will facilitate higher enrolment and study participation rates. As Victoria, Australia had one of the largest SARS-CoV-2 infection rates in Australia, it is supposed that there will be higher rates of LCS in this state. All study investigators have appropriate Australian professional registration and indemnity which will cover patient/clinician interaction in both states.

All studies will be undertaken in a quiet, dimly lit room with a comfortable ambient temperature between 21-24 degrees Celsius.

2.7 If research is to be conducted with or about participants living outside Australia outline any local legislation, regulations, permissions or customs that need to be addressed before the research can commence. Outline the steps taken to ensure that this has been adequately considered and addressed.

See *National Statement Chapter 4.8.* Attach authorising correspondence and/or approval documentation to the application. If you are travelling to a region classified as level 3 or 4 according to the Department of Foreign Affairs and Trade, travel approval may be required. See The University of Adelaide's travel safety information in the HSW Policy and Handbook.

n/a

SECTION 3: PARTICIPANTS AND RECRUITMENT

3.1 Who will be the participants in this project?

Participants also includes data about people or human tissue samples.

There will be three groups in this study:

1.Existing patients who have received treatment for POTS in accordance with established clinical guidelines who meet eligibility criteria will be enrolled;
2.Patients who have previously documented SARS-CoV-2 infection with subsequent unexplained chronic illness greater than 3 months will be recruited through Long Covid support groups on social media sites;

3.Healthy controls, age and gender matched

3.2 Does the planned or anticipated recruitment of participants target, focus on, or include as a group, any of the following population groups? Select as many as relevant.

This question is to capture the planned or foreseeable recruitment of participants from these population groups, rather than their incidental inclusion. Select as many groups as applicable to the research.

Participant group		Participant group	
Aboriginal and Torres Strait Islander people	☐	**People who may be involved in illegal activities**	☐

Children and young people	☐	**People with a cognitive impairment, an intellectual disability or a mental illness**	☐
Defence Force personnel	☐	**Primary or secondary school students**	☐
People highly dependent on medical care who may be unable to give consent	☐	**University students**	☐
People in dependent or unequal relationships	☐	**Women who are pregnant and the human fetus**	☐
People in other countries	☐	**None of these participant groups**	X

3.3 What is the number of participants?

Cohort One (LCS): 150 consecutive patients with LCS will be recruited from various social media and LCS support group platforms.

Cohort Two (POTS) 34 consecutive patients with POTS will be recruited from a speciality POTS clinic run by Dr Dennis Lau who is an Assoc/Prof at The University of Adelaide, Centre for Heart Rhythm Disorders

Cohort Three (Controls): 34 healthy, matched age and gender controls will be recruited from University and private medical campuses.

A base sample size calculation can be made using the formula: n = (t2 x p(1-p))m2, where t=confidence level at 95%, p=estimated prevalence of POTS within an LCS sample and m is the relative precision. Using this formula, a sample size of 139 provides sufficient statistical power to estimate a proportion (10% POTS amongst LCS) with a precision of 5% at the 95% confidence level. The number is increased to 150 to allow for withdrawal from the study.

From Walker et al. 2013 paper, the following information was obtained: at 30 minutes of orthostatic time, Stand healthy group (N=15) had mean orthostatic change in heart rate 26 bpm + SE=4 (SD=SE*SQRT(N) = 15.5) and the Stand POTS group (N=15) had mean orthostatic change in heart rate 45 bpm + SE=5 (SD=SE*SQRT(N) = 19.4).[24] Using a two-sample Satterthwaite t Test assuming unequal variance, with alpha=0.05, two-sided test and SD=15.5 and 19.4, if was found that there was 80% power to detect a mean difference of 45-26=19 when using a sample size of N=15 per group. If there is expected to be 20% loss to follow up, then a total of (20/9)*30=66.66 so N=34 is required in each group (N=68 in total) The statistical software used was SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

3.4 What is the age range of participants?

>18 years old. Controls will be matched to age and gender of the POTS and LCS cohorts

3.5 If this research involves children under 18 years of age, describe how the researcher/s comply with the University's Child-Safe Environment Policy:

See *National Statement* Chapter 4.2. Specific requirements for research activities involving children are highlighted in Section 2.4 of the University's Child-Safe Environment Policy.

N/A

3.6 What is the participant selection and exclusion criteria?

See National Statement Chapter 3.1.14 – 3.1.15.

Inclusion Criteria
Cohort 1 (LCS): Adults aged ≥18 years old (male or female); Able to provide written informed consent; previous SARS-CoV-2 infection (As some Australians contracted SARS-CoV-2 in countries that did not undertake testing in the early stages of the pandemic, some participants will not have a diagnosis by PCR. Inclusion with physician confirmed Long Covid is consistent with worldwide research practices for Long Covid studies); continuing chronic symptoms persisting for ≥3 months post-acute COVID-19 infection and not attributable to an alternative disease state.

Cohort 2 (POTS): Adults aged ≥18 years old (male or female); POTS diagnosis; Able to provide written informed consent; Diagnostic criteria for POTS met as per the following: 1. sustained heart rate elevation of ≥30 beats/min within 10 minutes. 2. No other secondary cause of these symptoms. 3. Absence of orthostatic hypotension 4. Symptomatology present for greater than 3 months

Cohort 3 (Healthy Control): Otherwise, healthy adults aged ≥18 years old (male or female); Able to provide written informed consent; absence of POTS diagnosis or previous SARS-CoV-2 infection.

Exclusion:
Non-consent for participation in study; pregnancy or lactation; other known causes of autonomic dysfunction; co-morbidities such as Type 1 Diabetes, Parkinson's disease, multiple sclerosis, alcoholism, drug addiction, malignant neoplasm, recent cerebrovascular accident or transient ischaemic attack, acquired brain injury; significant surgery within the last 3 months; unavailability for completion of all assessments as per the study protocol; non-English speaker; terminally ill with life expectancy <12 months.

3.7 Where will participants be recruited or sourced from?

Any use of snowball sampling for recruitment should only be in the passive form. That is participants may be asked to discuss the research with friends/contacts who they think may be interested in volunteering to be participants. Those new participants should then contact the research team to volunteer.

Participants will be recruited through social media forums that pertain to support of those with LCS. Administrators of social media platforms for LCS will be approached by senior investigators for permission to post information about the study with contact details for researchers. We recognised the selection bias associated with this method of recruitment, however given the extraordinary nature of the current pandemic and the lack of understanding of LCS and its associated diagnosis and aetiology, it would seem that this bias is justified by the urgent requirement for preliminary understanding of the condition. As this study looks to explore immune, inflammatory and cardiovascular changes rather than efficacy of interventions, the use of convenience sample is more tolerable.
In addition, consecutive patients with POTS who attend Dr Dennis Lau's practice and The University of Adelaide, Centre for Heart Rhythm Disorders will be recruited. Potential participants may be approached by a member of the clinic/study staff via email introducing the study and providing the plain language patient information sheet explaining the purpose of the study. Healthy controls will be recruited through flyers and posters placed within The University of Adelaide health and education campuses. In addition, healthy controls referred to CHRD/CVC for investigation of heart arrythmia (but found to have none) will be recruited via the above mentioned flyers. Advertisements will be placed on the SAHMRI and University of Adelaide facebook sites as per attachment 5.

3.8 What materials will be used to recruit participants and how will they be used?

Provide details of any posters, flyers, participant information sheets, consent forms, advertisements, emails and letters that will be used. Include a listing of any online or physical sites the advertisements will be posted. See *National Statement Chapter 3.1.20.*

POTS participants

- Email detailing study outline will be sent to potentially eligible participants. PICF will be attached to the email and patients will be requested to make contact if they are interested in the study.
- University social media and private practice internet advertisements
- Private practice and university flyers (attachment 6)

LCS participants

- Through social media advertisement (attachment 4)

Healthy matched controls will be recruited from

- Patients referred for cardiac evaluation who are healthy via practice flyers (attachments 6)
- Through flyers located at the Centre for Heart Rhythm Disorders facilities in Norwood, Adelaide and North Terrace Campus, University of Adelaide and SAHMRI (attachment 6)As well as facebook pages monitored and run by these organisations to promote current research.

Recruitment Materials: The following materials will be used to recruit participants.

1. Participant Information Sheet in plain language
2. Patient Consent Form
3. Introductory email to POTS patients who attend our private clinic
4. Introductory email and advertisement for social media administrators of support group for those with Long Covid
5. University of Adelaide, SAHMRI and Private Practice internet advertisements
6. Flyers for University and Private Clinic advertisement

3.9 How and by whom will initial contact with participants be made?

If recruitment is to be conducted by a third party, please describe how this will take place. Any use of snowball sampling for recruitment should only be in the passive form. That is participants may be asked to discuss the research with friends/contacts who they think may be interested in volunteering to be participants. Those new participants should then contact the research team to volunteer.
It is generally preferred initial contact is made in low pressure ways, such as email or post. If the initial approach will be made in another way, e.g. face to face, provide a justification.

Researchers named on this application will screen the Centre for Heart Rhythm Disorders POTS database for patients who attend the POTS clinic and who may meet the inclusion criteria. Those identified from the clinic as potential participants will be invited by email (See attachment 3). Some of the participants will be known to investigators through clinical practice. Potential participants will be provided with plain language statements (see attachment 1) explaining the purpose of the study and the benefits and/or risks of involvement. They will be given opportunity to discuss with family and support persons and invited to contact the research team for more information before making a decision to participate.
Those with LCS who respond to social media notices (see attachment: 4) requesting more information will be sent a plain language statement by Marie-Claire Seeley (PhD Candidate) via email and invited to discuss the study by telephone with a senior investigators before making a decision to consent to participation. Once this has been done formal arrangements for an appointment will be made for consent and enrolment in this study.
A description of the study will be placed on the University of Adelaide, Centre for Heart Rhythm Disorders and SAHMRI internet site as well as social media sites. (See attachment 5). Flyers will be placed at the Cardiovascular Centre Private Clinic as well as appropriate spaces at the University of Adelaide notice boards (See attachment 6). Those who respond to these advertisements via email will be sent a study PICF and offered an opportunity to discuss via phone with researchers.

3.10 Will any personal information including names, contact details, email addresses of participants etc. be accessed for purposes of recruitment? If yes, outline how and by whom this information will be accessed:

Researchers must ensure that personal information is not accessed without the consent of the individual.

Only patients who have registered and seen a cardiologist at The Centre for Heart Rhythm Disorders will be contacted using contact details patients have already registered with the Centre. These details will only be accessed by the researchers in this study (who work at The Centre for Heart Rhythm Disorders). Recorded details will remain on site and will not be removed.

In the cases of volunteers as controls and LCS cohort; they will contact the researchers and provide

consent for their details to be stored at The Centre for Heart Rhythm Disorders on a secure, password protected database.

3.11 Describe how, when and what information about the proposed research activities will be provided to participants and any third parties:

A person's decision to participate in research must be based on sufficient information, an understanding of research and the implications of participation. Use of the participant information sheet (which includes contacts for complaints) and consent form templates which cover the information required by the *National Statement* is required. For online surveys, the information sheet must be incorporated into the survey preamble. Where research is being conducted overseas, it would be helpful to participants if a local, 'independent' person is also included as a contact for complaint. These documents are to be attached to the application. See *National Statement Chapter 2.2*.

Potential study participants will be provided with a participant information sheet (See Attachment 1) via email or during a visit to the POTS clinic. Participants will be encouraged to discuss the involvement in the study with family and support persons before returning a signed consent form to the principal researcher. Participants will also be given the opportunity to ask direct questions of researchers in regard to participation, before deciding to consent to involvement in the study. All, participants will be familiarised with the facility and given further opportunity to ask questions when they arrive for the study. They will be given another opportunity to withdraw from the study after they have been familiarised with the protocol. Participants will be reassured that withdrawal will not affect continuation of medical treatment.

Please see attached participant information sheet and consent form. (Attachment 1 and 2 respectively)

3.12 How and when will consent be obtained from participants and any third parties?

See *National Statement Chapter 2.2 and Chapter 3.1 Element 3.* Templates for consent forms should be modified to suit the nature of the project.

Those who indicate an interest in participating in the study will be emailed a plain language information sheet and consent form. Additionally, they will be provided an electronic link to the REDCap patient information sheet and Consent Form. The consent form will only be accessed through the patient information sheet to ensure this information is read prior to electronic consent. Participants may choose whether to use the hard copy form or the electronic clinic provided.

Participantswill be given time to read the form and discuss with family and/or support persons before responding with their interest. Those who do not respond will be contacted no more thantwice by email or telephone after which they will be deemed not interested in study participation.

The POTS-LCS investigators will be available to review the informed consent form with potential participants upon request and address any questions or concerns prior to obtaining written informed consent for POTS-LCS participation.

Consent for future use of blood samples drawn during this study for POTS related research will be included on the Patient information and consent form. The investigators will also address any future questions or concerns of POTS-LCS participants.

Signed consent forms will be kept on record and a note in the patient's medical file (if a patient of the CHRD) will be made indicating their desire to be involved in the study. Institutional ethics and study approval will be informed by policies of the National Health and Medical Research Council of Australia and will be secured from the University of Adelaide, Human Research Ethics Committee before commencement of the trial, in accordance with humane experimentation requirements.

3.13 For participants not fluent in English or who have difficulty understanding English, what arrangements will be made to ensure comprehension of the research information?

N/A

3.14 Will the researcher(s) be taking photographs or recordings of participants using audio tape, film/video, or other electronic medium? If so, how will these be used?

This information should be provided to participants in the participant information sheet and the consent form.

No such data will be used for the study

3.15 In reference to Question 2.5, indicate all research activities in the study and where applicable outline the approximate time commitment required of participants.

Consult the definitions of research methods for guidance on selecting the method(s) applicable to the project:

Research method/activity		Participant time	Research method/activity		Participant time
Action research	☐		**Interventional**	☐	
Biospecimen analysis	☐		**Interview**	☐	
Body organs, tissues or fluids	☒	24hr urine collection	**Observational**	☒	75 minutes
Clinical Trial	☐		**Phlebotomy (Blood sampling)**	☒	10 minutes
Data linkage			**Survey**	☒	30 min at leisure
Drugs or isotopes If this is selected, a Drugs to be Administered Form is to be completed.			**Textual analysis** (including medical records, academic records, personal documents)	☐	
Epidemiological	☐		**Use of data sets**	☒	Oz POTS
Ethnographic	☐		**Other**	☐	
Focus group	☐				

3.16 Provide a description of each of the activities selected above in terms of what the participant will experience from taking part in the research:

Provide a summary of the focus of any research activities e.g. topics of the survey, interviews etc. and the format they will be undertaken e.g. face to face, online etc. If there are multiple methods, outline if participants are being asked to do one or all of the activities. Attach copies of surveys, interview or focus group schedules, questions and topics to be covered to the application. All attachments should be clearly labelled with appropriate headings and referred to within the body of the application.

Before study testing day:

In addition, all study participants will be sent a link to a health questionnaire and QoL surveys as listed below. These can be done at leisure and without time restriction to reduce the effects of inconvenience and survey fatigue.

1. Holter Monitor: All patients will undergo 24 hour ambulatory ECG, at home (adhesive electrodes placed on the skin and attached to a recording device). This measure will be used to determine heart rate variability; which is a measure of baseline autonomic tone. It will also help to exclude other alternative cardiac arrhythmias.
2. Echocardiogram requires the subject to undertake an ultrasound of the heart previous to the day of testing at the subject's convenience. This test is important for determining other secondary causes of symptoms due to structural cardiac changes. It requires a non-invasive ultra-sound of the heart and generally takes 15 minutes to complete. To determine associations of neuroendocrine function with changes to orthostatic filling volumes and cardiac measurements. Echocardiogram will be undertaken in the semi-fowler position and then in passive leg raise (45 degree) position after 90 seconds.
3. Demographic survey and Medical Health History including alcohol consumption, tobacco use. Past medical history, medications and allergies will be completed by the two symptomatic cohorts.

Controls will complete a health history and demographic survey to confirm absence of exclusion medical conditions and medications when attending for assessment.

4. Rand SF-36: 36 item short form survey which is commonly utilised to measure self-reported quality of life measures in adult patients.
5. EQ-5D/5L: Is a short survey utilised and validated to describe and value health across 5 domains.
6. COMPASS-31: 31 question composite autonomic scale which is utilised widely for use in autonomic research and practice. It addresses the domains of: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder and pupillomotor function.
7. Fatigue Severity Score: A 9 item questionnaire that reports how fatigue interferes with certain activities and rates the severity of fatigue.
8. 5 Point hypermobility screen: Five questions related to hypermobility. A score >2/5 suggests hypermobility (sens 85%, spec 90%)
9. Orthostatic Hypotension Questionnaire: A validated tool used to determine the burden and severity of orthostatic hypotension. It has two components: a 6-item symptom assessment scale and a 4 item activity scale.
10. Hospital Anxiety Depression Scale: 14 item scale with 7 items relating to anxiety and 7 to depression. A cut off score of 8 in either domain has been widely validated as a reliable indicator of anxiety or depression.

Study Day Testing

1. Physical assessment including vital signs, height, weight and BMI. 5 minutes
2. Valsalva manoeuvre is used to assess normal or disordered autonomic control of blood pressure and heart rate. The test requires the maintenance of forced expiration against resistance for 15 seconds and beat to beat, non-invasive blood pressure and heart rate monitoring. 5 minutes
3. Deep breathing test requires the subject to breathe at 6 breaths per minute while undergoing non-invasive 'beat to beat' blood pressure and heart rate monitoring to determine cardiovagal function. 10 minutes
4. Sudomotor function testing requires the subject to place hands and feet on SUDOSCAN metal plates. Reverse iontophoresis and chronoamperometry are used to assess chloride ion concentration of the skin which represents a measure of sudomotor output. This test is painless and non-invasive and requires the subject to stand still for 3 minutes while the SUDOSCAN assesses function. 5 minutes
5. Orthostatic challenge requires the subject to lay supine while 'beat to beat' non-invasive BP and HR recordings are taken. The subject then stands still for 10 minutes and changes in BP and HR are monitored. 12 minutes
6. Blood Draw: Subjects will undergo standing blood draw of 15 ml (3 teaspoons).
7. CANTAB cognitive testing requires the participant to complete a series of neurocognitive tests (CANTAB: Cambridge Neuropsychological Test Automated Battery, Cambridge Cognition Ltd.) to assess executive function, reaction time, memory, and attention. This testing is undertaken in the seated position, using an IPAD. The assessment time is approximately 30 minutes and includes the following tests:

    - Memory:
      Delayed Matching to Sample which assesses visual matching ability and short-term visual recognition memory.
    - Executive Function:
      Multi-tasking Test which assesses the subject's ability to manage conflicting information and to ignore task-irrelevant information.
    - Attention and Psychomotor Speed:
      Reaction Time: which assesses motor and mental response speeds, as well as measures of movement time, response accuracy, reaction time, and impulsivity.

Rapid Visual Information Processing which is a measure of sustained attention

8. 24 hr Urinary volume, sodium and osmolarity: At the end of their testing subjects will be given a container and a measuring pot to undertake a 24hr urine sodium, volume and osmolality study. This urine sample will be returned to a designated pathology collection centre the following day.

Information provided in **Question 3.16** should be incorporated into information provided to participants, either through a participant information sheet or other methods as described in **Question 3.11**. University templates for participant information sheets, consent forms and a drugs to be administered form are available at https://www.adelaide.edu.au/research-services/oreci/human/applications/.

3.17 For research that involves the handling, storage, and/or disposal of human biospecimens, please detail below the protocols that will be followed to ensure *National Statement* requirements are met.

See *National Statement Chapter 3.2*.

(a) The burdens of the blood and urine collection on the donor(s) are justified by the potential benefits of this proposed research. POTS and LCS have a significant patient burden in terms of reduced quality of life and high community and health care burden. This study has the potential to elucidate biomarkers that inform understanding of disease aetiology, diagnosis and treatment
(b) Blood and urine collection will be undertaken via a qualified and registered pathology collection service as well as by clinically trained and qualified researchers. These researchers include medical doctors and registered nurses who are experienced in the practices of safe blood collection and will adhere to best practice guidelines for phlebotomy. All blood tests will be undertaken in an appropriate clinical setting.
(c) Blood specimens will be deidentified, spun in a centrifuge and frozen and stored in locked bio-secure freezers at the South Australian Health and Medical Research Institute to facilitate analysis.

Routine blood and urine samples will be processed in accordance with current guidelines as detailed by the associated pathology group. Blood and urine samples will be labelled with the participants identifying information and then sent to the lab for processing. Once processed, identifying information will be exchanged for a code before results are returned to researchers to ensure de-identification.

Blood sample analysis undertaken by the researchers are detailed below**.** The principal investigator will be responsible for the permanent and safe disposal of samples as per University of Adelaide policies that govern safe handling of bio-specimens.

1. ELISA kits to detect autoantibodies against the α1 adrenergic b-1 adrenergic, M1 receptors and M4 muscarinic cholinergic receptor antibodies will be purchased form CellTrend GmbH (Luckenwalde, Germany). Samples will be processed as per the manufacturer's instructions.
2. Inflammatory biomarkers will be processed using ProcartaPlex™ Multiplex Immunoassay as per manufacturer's instructions.
3. Copeptin: Morning blood test with a 8 hr food fast (drink to thirst). Plasma will be collected in EDTA tubes, centrifuged and kept in -80 degrees freezer before batch analysis using the Thermo Scientific B·R·A·H·M·S Copeptin proAVP KRYPTOR assay using B·R·A·H·M·S KRYPTOR compact PLUS, Hennigsdorf, Germany). All data will be deidentified and stored as per above procedures. 5 minutes.

d) The principal investigator will be responsible for the permanent and safe disposal of samples as per University of Adelaide policies that govern safe handling of bio-specimens

SECTION 4: ETHICAL CONSIDERATIONS

In addition to the ethical considerations pertaining to all research participants, researchers should be aware of the specific issues that arise in terms of the design, conduct and ethical review of research involving various categories of participants as outlined in the *National Statement Section 4*.

4.1 Describe the likely burdens of participation and any risks to participants when undertaking the research:

Burdens include impacts on participants such as inconvenience e.g. filling in a form, participating in a street survey, or giving up time to participate in research and discomfort e.g. minor side-effects of medication, the discomforts related to measuring blood pressure, and anxiety induced by an interview. Risks can be emotional, social, legal, medical or physical and can include distress and harm. See *National Statement Chapter 2.1*.

Participation in the POTS-LCS involves potential risks of a breach of confidentiality of medical information and privacy of the participants.

As many participants will be known to the researchers, consideration must be given to the potential for participants feeling 'obligated' to participate in the study.

Some of the investigations such as blood samples and 24hr Holter monitors may cause some discomfort and inconvenience.

Orthostatic challenge tests may illicit symptoms such as dizziness and palpitations particularly in those with POTS. In susceptible patients, vasovagal syncope may occur, in which case the test will be terminated immediately, the patient offered medical assistance and then arrangements made for safe return home (arranging a family member to pick them up or providing a taxi home)

Some participants will be required to cease medications that currently control heart rate and reduce the effects of POTS on orthostatic intolerance. Those with a serious heart condition are excluded from this study therefore, medication that participants are currently on does not control a serious underlying cardiac condition but rather 'improves' functionality and quality of life related to POTS/Long Covid. It is likely that those on these medications will experience a decline in functionality and an increase in unpleasant orthostatic intolerance symptoms during the period of medication cessation.

Reimbursement for any reasonable travel, parking, and other expenses associated with the researcl project visit will be provided up to $30.

Quality of life questionnaires have the potential to trigger emotional responses particularly for those who are confronted by chronic illness.

4.2 Describe how the risks will be minimised or mitigated. Outline any relevant protocols for management of risks including distress protocols, occupational health and safety practices, first aid procedures etc.

See *National Statement Chapter 1.7 and Chapter 2.1.*

Breach of confidentiality:

If any researcher/investigator becomes aware of an actual or suspected data breach, they must report it as soon as possible to the Principal Investigator and custodian of the POTS-LCS. The Principal Investigator will respond as per the University of Adelaide Data Breach Response Plan by:

- recording the details of the data breach in the Data Breach Report Form provided in Schedule 1 (Data Breach Report);
- providing a copy of the Data Breach Report to their Area Manager either in person or by email; and

- otherwise keeping the incident confidential except where it is necessary to disclose information about the incident in accordance with this Plan.
- cooperate with the Area Manager to:
- Contain data breaches and remediate harm
- Preserve evidence of a suspected data breach
- Participate in a review of practices and response to the data breach

Coercion/Obligation:

Clinicians will not directly approach patients with a request to participate. Rather a study PICF will be emailed to patients by administration staff at the CHRD. Participants will then be able to consider the information and indicate their interest by responding via email or requesting a consent form from administration. This will also give the participants time to consider any questions they have in regard to the study. Participants will be given an opportunity to ask any questions of a senior investigator before signing the consent form. Participants will be informed that their medical care will not change in any way as a result of participation or declining to participate in the study.

Discomfort and Inconvenience

The PICF will clearly highlight the potential discomfort and inconvenience that may be involved in undertaking the autonomic testing, blood test and health related questionnaires. This ensures clear disclosure and may help to prepare participants for the expected experiences.

Cessation of medications that control heart rate and expand fluid volume will inevitably result in return of unpleasant orthostatic symptoms associated with POTS/LCS. These symptoms are generally not considered dangerous but will impede on functionality and can be severe for some individuals. This has been clearly articulated in the PIS which states:
"Some participants will be required to stop medications such as those that control their heart rate before the study day. This is so the researchers can detect differences in how your heart reacts to different tests such as the deep breathing test. Stopping these medications is likely to allow some of your symptoms such as dizziness and fast heart rate, return. This is likely to be unpleasant for you and may take some time to recover once you restart your normal medication."

Autonomic testing may illicit feelings of dizziness and general 'unwellness', particularly in those with POTS. For this reason, experienced clinicians will be in attendance at all participant testing sessions. First aid kits, comfortable, tiltable chairs, vital sign monitoring and fresh drinking water will be available for all participants. Any detrimental reactions to testing (such as fainting during blood draw) will be recorded and followed up with appropriate medical assessment by clinician/researchers. The PICF will recommend that participants are accompanied to testing by a support person in case of adverse effects of testing.

QoL surveys may be completed online through a secure link given to participants. This decreases the testing burden by allowing participants to respond at their leisure. This will reduce the associated inconvenience and will enhance completion and accuracy of outcomes. Contacts for psychological support will be detailed on the PICF should health related survey's raise issues of concern for participants

In addition, the procedure will be carried out at a registered medical practice and therefore poses minimal risk to the researcher. There is a small risk of needle injury from phlebotomy. This will be mitigated by usual OH&S practices of wearing gloves and disposing sharps in an appropriate manner. Other risks to researchers also relate to standard workplace occupational health and safety practices and are covered by University OH&S policies which are outlined during staff induction.

Please see below 4.3 for more details on how data/security risks will be addressed.

4.3 Describe how researcher(s) will protect the privacy and confidentiality of participants.

See *National Statement Chapter 1.6 and Chapter 2.1*

Identifiable information such as names, birthdates, contact details, and medical record numbers of the POTS-LCS participants will be deleted from their stored medical information and replaced with a linkage code. Access to participant medical information contained within secure University database will be restricted to study investigators.

Information linking the linkage codes to the participants' identifiable information will be stored in a secure location separate from the medical information. Access to the information linking the linkage codes with information that may identify participants will be granted only to CHRD investigators on a need-to-know basis as approved by the Principal Investigator of the POTS-LCS. Access to the information linking the linkage codes with participant identifiers shall be documented.

Participant physiological and health data will be electronically stored on a secure encrypted server at for a minimum of 10 years on a Centre for Heart Rhythm Disorders computer. Individual study patient data will be coded and stored in a non-identifiable way (code or number).

On withdrawal or when the minimum storage time has elapsed the principal investigator will be responsible for destroying the data by permanent deletion.

Blood samples will be coded in an unidentifiable way and stored at the locked laboratory at the South Australian Health and Medical Research Institute. Some blood and urine samples will be processed via an independent pathology group and results sent to the lead investigator. De-identification of the samples will take place before analysis. Patient details will be sent to the pathology service to allow for reporting of tests results to participant's local doctor. Should they consent and indicate this as their preference.

4.4 Describe how the likely benefits of the research will justify the burdens and/or risks to participants:

See *National Statement Chapter 1.6 and Chapter 2.1*

There are no direct benefits associated with participation in the POTS-LCS. The risks of this study are small and relate mainly to discomfort. However, the impact of chronic health burden of LCS and POTS on the young (predominately female) population around the world are significant for both the individual and society. The following benefits outweigh the risks stated. With the exception of the inflammatory biomarkers, every test undertaken in this study is routinely used in the clinical diagnosis, management and monitoring of POTS. The additional burden of testing is therefore limited for those with POTS and LCS.

Results from the study will raise awareness of dysautonomia in this post-viral cohort of patients and thereby may promote earlier diagnosis and appropriate management to achieve the best outcomes.

This investigation may dispel currently held beliefs of some clinicians that LCS and its associated symptoms may stem from psychological/neuropsychiatric elements akin to post traumatic distress
Studying the post-acute SARS-CoV-2 infection cohort will help improve the current understanding of POTS due to post-viral triggers and may be of future benefit to patients with POTS.

Findings of this study will improve overall recognition of POTS in the wider medical community as it remains under-recognized that has led to delayed diagnosis and suboptimal management as reported by many sufferers of this condition

4.5 Outline the protocol that will be followed in the event of any adverse events:

It is a condition of approval that researchers **immediately** report to the HREC Secretariat any adverse events that might warrant review of ethical approval. See *National Statement Chapter 5.1 and 5.5.*
In the event of any breach of data, The University of Adelaide's Privacy Management Plan and Data Breach Response Plan must be followed.

Data Breach
If any researcher/investigator becomes aware of an actual or suspected data breach, they must report it as soon as possible to the Principal Investigator of the POTS-LCS. The Principal Investigator will respond as per the University of Adelaide Data Breach Response Plan by:
(a) recording the details of the data breach in the Data Breach Report Form provided in Schedule 1 (Data Breach Report);
(b) providing a copy of the Data Breach Report to their Area Manager either in person or by email; and
(c) otherwise keeping the incident confidential except where it is necessary to disclose information about the incident in accordance with this Plan.
(d) cooperate with the Area Manager to:

- Contain data breaches and remediate harm
- Preserve evidence of a suspected data breach
- Participate in a review of practices and response to the data breach

In the case of an adverse event:

- Tests will be discontinued immediately
- Patients will be assessed medically and arrangements made for safe return home.
- If required arrangements for follow up will be made at the Cardiovascular Centre in Norwood or their local General Practitioner. These are unlikely scenarios given the nature of the testing protocol.
- The Director for the Centre for Heart Rhythm Disorders and supervisor of this project, as well as the treating GP will be notified of any adverse events.
- Any adverse events that might warrant review of ethical approval will be referred to the HREC secretariat.

4.6 Will participants receive any reimbursement of out of pocket expenses, or financial or other rewards as a result of participation? What is the amount or nature of the reimbursement/reward and the justification for this?

See *National Statement Chapters 2.2.10 - 2.2.11; 3.1.10 and 3.1.22.*

There are no additional costs associated with participating in this research project. You will not be out of pocket for any cost including those diagnostic studies such as the blood tests, Holter monitor and echocardiogram. The results of these will be available for you to keep. However, there is no formal monitory re-imbursement for your involvement in this study. Participants who are likely to face financial hardship due to travel costs are eligible to claim for a travel stipend up to $30 on production of receipts.

4.7 Does the research involve limited disclosure of the research aims? If YES, provide a justification.

See *National Statement Chapter 2.3.*

no

4.8 Describe any possible risks to the health or safety of the researcher(s) when undertaking the research?

Where interviews are to be held in participants' homes as opposed to public places provide a rationale other than convenience for why this is necessary (and outline the personal safety protocol for the researchers involved). See the *Australian Code of Responsible Conduct in Research 1.2.*

The study will be carried out at a registered medical practice and therefore poses minimal risk to the researcher. There is a small risk of needle injury from phlebotomy and all researchers involved in this will be clinically trained and experienced in phlebotomy. Risk will be mitigated by usual OH&S practices of wearing gloves and disposing sharps in an appropriate manner. Risk to researchers also relate to standard workplace occupational health and safety practices and are covered by University OH&S policies which are outlined during staff induction.

SECTION 5: DATA – CONFIDENTIALITY, ANALYSIS, REPORTING, STORAGE AND FUTURE USE

5.1 Select the option that reflects the type of data that will be accessed throughout the research:

For some research, the type of data received or collected initially may be different to the type of data that is stored. For instance, interview data with names recorded is individually identifiable data. If names are *permanently* removed when the data is stored at the completion of the project, the data will then be considered non-identifiable. Personally identifiable information is any part of someone's personal details which can be used to identify them as an individual. This can include name, birth date, home address, email, phone number and student ID. See *National Statement Chapter 3.1 Element 4.*

Type of data	Initially received/ collected	Stored (at completion)
Non-identifiable: data received or collected about participants that is received in a non-identifiable form. This includes data which has never had personal identifiers e.g. an anonymous survey, or from which identifiers have been permanently removed before you received it. **It is not possible for you to identify a specific individual.**		
Re-identifiable: data from which personal identifiers have been removed and replaced by a code. The data is either received with a code already attached and personal identifiers have been removed or you remove identifiers and replace with code. **It remains possible for you or others to re-identify a specific individual by, for example, using the code or linking different data sets.**	X	X
Individually Identifiable: data where the identity of an individual could be reasonably ascertained. Examples of identifiers include the individual's name, image, date of birth or address, or in some cases their position in an organisation.	X	

5.2 Compliance with the *Guidelines under Section 95 and 95A of the Privacy Act 1988:*

	YES	NO
5.2.1 Is this research relevant to public health or public safety, or to the management, funding or monitoring of a health service? This includes collecting, using or disclosing health information for the purposes of research or compiling statistics relevant to public health or public safety.	☒	☐
5.2.2 Does the research involve collection, use or disclosure of health information held by an organisation **without** consent from the individual(s) the information relates to?	☐	☒
5.2.3 Is the information you will be *accessing or collecting* individually identifiable? **i.e. the individual's identity can be reasonably ascertained.** Medical case notes would generally be considered individually identifiable.		☒

If you answer **YES** to all three questions in **5.2**, you will need to provide a proposal to the HREC as to why the public interest value of your research out-weighs the public interest in the protection of privacy. The proposal must address the appropriate sections of the *Guidelines under Section 95 and 95A of the Privacy Act 1988*. The guidelines are available at: https://nhmrc.gov.au/about-us/publications/guidelines-under-section-95-privacy-act-1988 and https://nhmrc.gov.au/about-us/publications/guidelines-approved-under-section-95a-privacy-act-1988.

In the questions below, outline how the privacy and confidentiality of participant data and samples will be protected throughout the different stages of the research, making reference to the type of data (non-identifiable, re-identifiable or individually identifiable) that will be accessed by the researcher(s).

5.3 How will the privacy and confidentiality of participant data, samples and information be protected during the collection and/or recruitment phase?

Outline the de-identification processes, separation of roles of those responsible for the management of data, and any other relevant practices. Outline where data will be stored during data collection phase and who will have access. See *National Statement Chapter 3.1 Element 4.*

Participant medical information will be stored electronically on an encrypted server within the Centre for Heart Rhythm Disorders. Identifiable information such as names, birthdates, contact details, and medical record numbers of the POTS-LCS participants will be deleted from their stored medical information and replaced with a linkage code. Access to participant medical information contained within the database will be restricted to CHRD investigators named on this protocol.

Information linking the linkage codes to the participants' identifiable information will be stored in a secure location separate from the medical information. Access to the information linking the linkage codes with information that may identify participants will be granted only to CHRD investigators named on this protocol on a need-to-know basis as approved by the Principal Investigator of POTS-LCS. Access to the information linking the linkage codes with participant identifiers shall be documented.

The data obtained from the autonomic testing protocol is purely physiological and not identifiable. It will be stored electronically on a secure encrypted server and retrieved for statistical analysis on a Centre for heart Rhythm Disorders computer. Individual study patient data will be coded and stored in a non-identifiable way (code or number).

Blood samples and primary materials will be stored by the principal investigator in the University of Adelaide CHRD locked laboratory at the South Australian Health and Medical Research Building, and recorded in the University's metadata store. All access to said samples will be approved by the Principal Investigator and logged in the study logbooks.

5.4 How will the privacy and confidentiality of participant data, samples and information be protected during the data analysis phase?

Outline the de-identification processes, use of pseudonyms, codes, or explicit consent, and any other relevant practices. Outline where data will be stored during data analysis and who will have access. See *National Statement Chapter 3.1 Element 4.*

Participant medical information will be stored electronically on an encrypted database at the Centre for Heart Rhythm Disorders. Access to this data will be limited to researchers listed on this application. No other parties aside from the personnel listed in this applicationwill have access to individual patient data during statistical analysis. No third parties will be included in statistical analysis.

5.5 How will participant data, samples and information be analysed and who will undertake this analysis?

Marie-Claire Seeley will perform the primary analysis of the physiological data with supervision from the listed researchers. Continuous variables will be reported as mean and standard deviation, or median and interquartile range, as appropriate to distribution. Count variables will be reported as numbers and percentages. Categorical variables will be evaluated using a chi-square or Fisher exact test as appropriate. All statistical tests will be two-sided, and a p value of <0.05 will be considered significant. All analyses will be undertaken using Stata 13.0 (Stata Corporation).

Some routine blood samples and urine will be analysed at a third party, accredited pathology service. The samples will be de-identified and coded in an unidentifiable way. No patient details will be sent to the pathology service. Blood sample analysis undertaken by the researchers detailed below at University of Adelaide Laboratories, SAHMRI. These samples will be analysed according to the following protocols.

- ELISA kits to detect autoantibodies against the α1 adrenergic b-1 adrenergic, M1 receptors and M4 muscarinic cholinergic receptor antibodies will be purchased form CellTrend GmbH (Luckenwalde, Germany). Samples will be processed as per the manufacturer's instructions.
- Inflammatory biomarkers will be processed using ProcartaPlex™ Multiplex Immunoassay as per manufacturer's instructions
- Copeptin: Morning blood test with a 8 hr food fast (drink to thirst). Plasma will be collected in EDTA tubes, centrifuged and kept in -80 degrees freezer before batch analysis using the Thermo Scientific B·R·A·H·M·S Copeptin proAVP KRYPTOR assay using B·R·A·H·M·S KRYPTOR compact PLUS, Hennigsdorf, Germany). All data will be deidentified and stored as per above procedures

5.6 What feedback of findings will be offered to participants e.g. access to transcripts of interviews, drafts or final reports? When will this occur? If no feedback will be offered, outline why.

It is good practice to provide participants with the opportunity to review any transcripts, particularly if they will be named or there is the potential for them to be identifiable in the research findings.

Individual results of exploratory biomarkers will not be used clinically and will not provide meaningful information to the individual. However, screening results from routine blood, urine, Holter monitor and echocardiogram results will be copied to participant's local doctor at the participant's request, as these may be clinically meaningful and valuable for comparison in later treatment or assessment.

Participants will be emailed a link to any publications eventuating from this study.

5.7 How will the project outcomes be made publicly accessible at the end of the project and in what forms (e.g. journal article, book, conference paper, in the media, presentations)? If they will not be made publicly accessible, explain why.

The aggregate results will be disseminated by way of presentation at local or national medical/scientific conferences with the aim of publication of our findings in a relevant cardiovascular journal.

5.8 How will researcher(s) protect the privacy and confidentiality of participant data, samples and information during the reporting of research results?

Outline if participants will have the option of being identified or referred to by a pseudonym. Where the sample size is very small, it may be impossible to guarantee anonymity/confidentiality of participant identity. Participants involved in such projects need to be clearly advised of this limitation in the information provided to participants. See *National Statement Chapter 3.1 Element 5, and Chapters 3.1.41 and 3.1.61.*

No identifiable data will be published. Individual physiological responses may be presented as samples but this will not be identifiable to any individual. No condition being assessed is of such a rare type that will allow for unintended identification of the individual.

5.9 Outline how the records, materials and data from the project will be stored at completion. Include details of the storage location, who will have access.

Refer to Section 2 of the *Australian Code for the Responsible Conduct of Research*.

Project data will be stored and hosted by The CHRD, University of Adelaide,

Non-digital research data and primary materials will be stored by the principal investigator in the University of Adelaide CHRD locked laboratory at the South Australian and Medical Research Building, and recorded in the University's metadata store. All access to said samples will be approved by the Principal Investigator and logged in the study logbooks.

Accurate, complete, reliable, and authentic records of research methods, data, materials and findings, including any approvals will be maintained for a minimum of 10 years. These records will be kept in an organised and accessible format in a password protected University of Adelaide 'Box' along with associated metadata.

5.10 Who will be the data custodian?

All data collections should have an identified custodian to enable access by researchers or participants to the data while maintaining it in a protected form. The custodian of the data may be the individual researcher or agency who collected the information, or an intermediary that manages data coming from a number of sources.

Please note for student projects the data custodian must be the Principal Supervisor ('Applicant').

See *National Statement Chapter 3.1.55*.

The Principal Investigator Assoc/Prof Dennis Lau is the custodian of the data and is responsible for destruction of the data.

5.11 Outline the length of time that the records and materials will be retained by the University.

Note that the minimum period for retention of research data is 5 years from the date of any publication and varies depending on the specific type of research. For more information refer to the University of Adelaide's Research Data and Primary Materials Policy and Section 2 of the *Australian Code for the Responsible Conduct of Research*.

Paper records of patient details will be kept for 5 years at the Centre For Heart Rhythm Disorders, Cardiovascular Centre, Norwood. Electronic data will be kept for 10 years and University encrypted and password protected Box, REDCap and U Drive platforms. Blood and urine samples collected by third party pathology groups will be destroyed after processing as per institutional guidelines. Blood samples stored at the University of Adelaide secure laboratories will be stored for a minimum of 5 years. Disposal of biospecimens will be done in accordance with any institutional health and safety requirements and in respect of any socio-cultural, culture or religious considerations that may be raised.

5.12 What type of consent will be obtained? Will consent be Specific, Extended, or Unspecified?

Data collected as part of a research project ought to be collected and stored in such a way that it can be used in future research projects. Data collected as part of a research project can only be shared or used in future with the explicit consent of participants. The participant information sheet and consent forms must outline how data will be shared or used in future. You cannot share or use data in future if you do not have consent to do this. See *National Statement Chapter 3, particularly 'Sharing of Data and Information'.*

For definitions of types of consent see the *National Statement Chapter 2.2.14*.

Unspecified consent will be obtained and is clearly identified and described in the Participant Consent form.

5.13 If Specific Consent is sought, justify why the data and information generated by this research should not be made available for future research:

Where a researcher believes there are ethical reasons not to make research data or information accessible for future use, this must be justified. See *National Statement Chapter 3.1.50.*

n/a

5.14 Describe what data will be used in future, how it will be used (i.e. for what purpose), who will have access and how participants will be informed. Outline how data will be shared.

If future use or sharing of the data is intended, participants are to be fully informed of this in the Participant Information Sheet and Consent Form. For more information see *National Statement Chapters 2.2.14 - 2.2.18 and 3.1.45(i).*

Data will be uploaded to 'Figshare' for international collaborative research use. No identifiable information will be shared. Remaining biospecimens will be stored for future use as per the patient consent form which asks for unspecified consent. There is no intention or request of participants for use of their samples for exportation. Biospecimen data will remain re-identifiable to allow future contact in regard to important findings relating to their samples. As per The University of Adelaide's policy. No data will be released to other third-party researchers without permission from the chief investigator and appropriate institutional ethics approval has been granted. Institutional ethics will be sought and received before any samples may be used for said research. All data may only be used in a manner that is appropriate to the informed consent received from participants.

SECTION 6: CONFLICT OF INTEREST OR OTHER ETHICAL ISSUES

6.1 Outline the source of any project funding:

See *National Statement Chapter 5.2.8*

The Centre for Heart Rhythm Disorders has funds already available for use. Marie-Claire Seeley (PhD Candidate) is supported by the University of Adelaide Divisional Scholarship. Assoc/Prof Dennis Lau is the recipient of $100 000 US grant from Standing up to POTS (USA) for this project.

6.2 Outline any 'conflict of interest' issues that may arise during the project:

See *National Statement Chapter 5.2.11 and Chapter 5.4*

Assoc/Prof Dennis Lau holds positions with the Centre for Heart Rhythm Disorders, Adelaide University as well as at The Royal Adelaide Hospital, CALHN.

6.3 Do the researchers expect to obtain any direct or indirect financial or other benefits from conducting this research?

Benefits must be declared to the HREC and included in the information provided to participants. See *National Statement Chapter 5.4.*

There are no direct or indirect financial benefits to declare.

6.4 Outline any other ethical or relevant issues not yet discussed in this application:

There are none identified

SECTION 7: RESEARCHER(S)' QUALIFICATIONS AND EXPERIENCE

7.1 Student Researcher(s):

This section should be completed for all students listed in Question 1.6. If there will be direct contact with participants by the research student/s, outline their experience and training to conduct this research.

Student's name, title:	Marie-Claire Seeley	**School or Department:**	School of Medicine
Program Level: PhD, Masters by Research/Coursework, Bachelor, Honours etc.		PhD	

Email:	Marie-claire.seeley@adelaide.edu.au	**Phone:**	0438392919
Qualifications and research experience relevant to the project:	Marie-Claire Seeley is a Clinical Nurse (RN, MN) with extensive experience in patient assessment and management of Postural Orthostatic Tachycardia Syndrome. Marie-Claire currently runs a nursing clinic for patients with this syndrome. Previous roles as an Emergency Department Assistant Unit Manager, Clinical Educator and Risk Committee Member means that she has extensive experience in patient assessment and data management. All of which are relevant to this project.		
Role in the research:	Primary Student Investigator		
Student's name, title:	Marie-Claire Seeley	**School or Department:**	Centre for Heart Rhythm Disorder
Program Level:		If other please describe	PhD
Email:	Marie-claire.seeley@adelaide.edu.au	**Phone:**	0438392919

Student's name, title:	Erin Welford	**School or Department:**	School of Nursing
Program Level: PhD, Masters by Research/Coursework, Bachelor, Honours etc.		Honours (Nursing)	
Email:	A1720832@student.adelaide.edu.au	**Phone:**	
Qualifications and research experience relevant to the project:	Erin is an RN who currently works in Cardiology Ward practice at Calvary Adelaide. She is currently an enrolled Honours of Nursing student and will be undertaking her research project with the Centre of Heart Rhythm Disorders in Adelaide. She has an interest in Postural Orthostatic Tachycardia Syndrome due to her exposure to this patient cohort in Cardiology practice and will use her Honours year to further explore this complex condition and its impact on health outcomes.		
Role in the research:	Student investigator		

7.2 Other Researcher(s):

This section should be completed for all researchers listed in Question 1.7.

Name, title and position:	Dr Celine Gallagher, RN, PhD	**School/Department or other institution:**	Centre for Heart Rhythm Disorders
Email:	celine.gallagher@adelaide.edu.au	**Phone:**	83139000
Qualifications and research experience relevant to the project:	Celine completed her PhD in 2019, which explored the role of alternative models of care delivery and cardiovascular risk factor management to improve outcomes in atrial fibrillation. In recent times she has developed an interest in the management of autonomic dysfunction and specifically Positional Orthostatic Tachycardia Syndrome. She is a co-author of a review of management strategies for this condition and is currently supervising a number of projects exploring mechanisms to improve outcomes in this population. She has co-authored a total of 37 peer reviewed publications and has been awarded $275,000 in competitive grant funding.		
Role in the research:	Co-Investigator		

Name, title and position:	Dr Adrian Elliott	**School/Department or other institution:**	Centre for Heart Rhythm Disorders
Email:	Adrian.elliott@adelaide.edu.au	**Phone:**	83139000
Qualifications and research experience relevant to the project:	Adrian is a Heart Foundation Future Leader Fellow and a Senior Lecturer in the Adelaide Medical School. He obtained his PhD in cardiovascular physiology and has published over 50 manuscripts relating to the management of arrhythmias, including POTS. His expertise includes exercise testing, cardiac imaging and autonomic assessments.		
Role in the research:	Co-Investigator		

Name, title and position:	Dr Tilenka Thynne	**School/Department or other institution:**	Flinders Medical Centre
Email:	Tilenka.thynne@sa.gov.au	**Phone:**	(08) 8371 2229
Qualifications and research experience relevant to the project:	Dr Thynne is a Clinical Pharmacologist and Endocrinologist working as a staff specialist in a tertiary teaching hospital, Flinders Medical Centre, in Southern Adelaide, Australia. She is a fellow of the Royal Australian College of Physicians. She is a lecturer in the Division of Medicine, Flinders University, Adelaide, Australia. Dr Thynne brings her clinical experience as an endocrinologist to this project with expertise in the use of DDAVP for the treatment of Diabetes Insipidus and the use of dynamic testing and copeptin as a biomarker in this setting. She has clinical research trial experience in a medical consultancy role and as a sub-investigator for CMAX clinical trial unit, Royal Adelaide Hospital, Australia – a clinical trial unit conducting trials ranging from phase 1 to 3. As a member of the Southern Adelaide Clinical Human Research Ethics Committee and previous member of the Investigational Drug Subcommittee of the Royal Adelaide Hospital Research Ethics Committee, she has extensive experience in evaluating trial design and safety. She is an expert reviewer and author for the Therapeutic Guidelines (an independent Australian not-for-profit organisation dedicated to deriving guidelines for therapy from the latest world literature) in Endocrinology (2012-2013) and Diabetes (2019). She has a strong focus on the Quality Use of Medicine and Medication Safety and is the co-chair of the Southern Adelaide Local Health Network Medication Safety Committee. She has co-authored a total of 20 peer reviewed publications.		
Role in the research:	Co-Investigator		

SECTION 8: DECLARATION BY THE RESEARCHER(S)

8.1 Readability Review:

Readability is the ease with which text can be read and understood. Applications are sometimes delayed when corrections due to issues with readability, especially to the participant documents (Information Sheets, Consent Forms, surveys etc.) are needed. Grammar, technical terms and language not tailored to the participant can impact on participants' understanding of the research and being able to give fully informed consent. A review for readability involves asking someone (other than the author) such as a peer outside the research team to review the application and participant documents for feedback on the ease to which the application and participant documents were read and understood. For students, the Writing Centre can provide assistance with the expression of participant documents.

Has the application, including the participant documents, undergone a readability review?	Yes ☒	No ☐

8.2 Declaration by the Researcher(s):

I/we have read the *National Statement on Ethical Conduct in Human Research 2007 (Updated 2018)* and the ***Australian Code for the Responsible Conduct of Research*.**

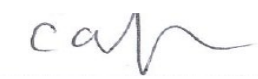
I/we, the researcher(s) agree to:

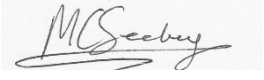
- conduct the project in accordance with our responsibilities under the *National Statement on Ethical Conduct in Human Research (2007)* and the *Australian Code for the Responsible Conduct of Research*
- start this research project only after obtaining final approval from the Human Research Ethics Committee (HREC)
- only carry out this research project where adequate funding and personnel is available to enable the project to be carried out according to good research practice and in an ethical manner
- notify the HREC in writing in the event of any adverse or unforeseen events; requesting amendments for approval prior to commencement; completion; discontinuation of the project or changes to research personnel
- provide an annual progress report to the HREC for the duration of the research project
- provide the HREC with a final report
- agree to participate in an audit if requested by the HREC.

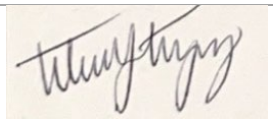
In addition, as the applicant, I:

- accept responsibility for the conduct of this research project in accordance with the *National Statement on Ethical Conduct in Human Research 2007 (updated 2018)* and the *Australian Code for the Responsible Conduct of Research.*
- certify that all researchers and other personnel involved in this project are appropriately qualified and experienced or will undergo appropriate training and supervision to fulfil their role in this project
- will take responsibility for the confidential maintenance of the research materials as per the University's Responsible Conduct of Research Policy, the University's Records Policy, the University's Research Data and Primary Materials Policy and as required by legislation.

All persons named in **Section 1** are required to sign below:

Applicant's signature:		Name:	Assoc/Prof Dennis Lau	Date:	18/03/21
Researcher's signature:		Name:	Dr Celine Gallagher	Date:	18/03/21

Researcher's signature:		Name	Adrian Elliot	Date:	18/03/21
Researcher's signature:		Name:	Marie-Claire Seeley	Date:	18/03/21

Researcher's signature:		Name:	Erin Welford	Date:	18/03/21
Researcher's signature:		Name:	Tilenka Thynne	Date:	18/03/21

SECTION 9: CHECKLIST

The following documents are attached to this application:

All documents attached should be referred to in the main body of the application and clearly labelled using appropriate headings i.e. Attachment 1, Attachment 2 etc.

Documents should also be labelled with a version number and a date.

Yes	No	N/A*	Item	Attachment Label (attachment 1 etc.)
☒	☐	☐	Participant information including contacts for complaints: either as information sheet, verbal script or survey preamble	1
☒	☐	☐	Standard Consent Form for a participant in a research project (written consent is required for the majority of projects)	2
☐	☐	☒	Consent by a Third Party to Participation Form (required where participants are children under 18 years or a dependent adult)	
☒	☐	☐	Other recruitment documentation including advertisements, flyers, recruitment letters, emails of introduction, copy of Facebook event pages and social media event sites.	3-6
☐	☐	☒	Procedure/protocol for interviews or focus groups including topics, questions or themes	
☒	☐	☐	Survey instrument/Questionnaire (include a printed copy of on-line survey)	7
☐	☐	☒	Adverse events procedure	
☐	☐	☒	Evidence of approval/rejection by other HRECs, including comments and requested alterations to the application	
☐	☐	☒	Research with people outside Australia: Evidence of permissions, approvals from overseas authorities etc.	
☐	☐	☒	Administration of Drugs Form	
☐	☐	☒	Annual Report on Project Status (if extending project)	

*Not applicable

SECTION 10: HOW TO SUBMIT THIS APPLICATION

1. Print the completed form and obtain signatures from all researchers.
2. Scan the signed form including all labelled attachments as **one pdf file** and email to: hrec@adelaide.edu.au. (Low Risk Applications in the School of Psychology should be sent to the chair of the review subcommittee).
3. Submission deadlines apply to applications requiring full HREC review. Applications for low risk review can be submitted at any time. Research timetables should allow for the possibility that a project submitted as a low risk application may be deemed to involve more than low risk, or to raise other issues, therefore requiring full review. Researchers may be requested to provide additional information.

NB References to the *National Statement* throughout the application form are not meant to be exhaustive but rather they aim to provide a starting point for researchers to consider. Researchers should be familiar with the *National Statement* and other relevant guidelines.

Attachment One: PARTICIPANT INFORMATION SHEET

PROJECT TITLE: Postural orthostatic tachycardia syndrome (POTS) in Long COVID syndrome: A detailed profiling study (POTS-LCS)

HUMAN RESEARCH ETHICS COMMITTEE APPROVAL NUMBER: H-2021-053

PRINCIPAL INVESTIGATOR: Associate Professor Dennis Lau

STUDENT RESEARCHER: Marie-Claire Seeley

STUDENT'S DEGREE: PhD

Dear Participant,

You are invited to participate in the research project described below.

What is the project about?

This research project is about the prevalence of autonomic nervous system dysfunction in those who have chronic health problems after SARS-CoV-2 infection. It will also look at the symptoms and blood profile of people with 'Long Covid Syndrome' (LCS) and postural orthostatic tachycardia syndrome (POTS) to see if there are common signs of inflammation or immune involvement in their symptoms. We aim to determine if there is an association of these blood and urine markers with symptoms such as fatigue, fast heart rate, breathlessness and dizziness. We think this is very important because identifying the role of inflammation and immunity in these disorders can hopefully provide better treatments for those with POTS and LCS

We are enrolling patients with LCS (>3 months of unexplained, lingering symptoms after Covid-19 infection) as well as patients with POTS (diagnosed by a doctor) and healthy adults over the age of 18.

We shall perform the following tests in one visit to measure the heart responses to changes in the volume of blood in the heart:

- *We will take your blood pressure, temperature and heart rate and will measure your height and weight*
- *We will look at your blood pressure and heart rate response to deep breathing and Valsalva Manoeuvre (blowing out against a force similar to when blowing up a balloon)*
- *We will look at your body's response to standing still for 10 minutes*
- *We will test your body's sweat response in the hands and feet*
- *We will look at your brain's ability to concentrate, pay attention and remember information*
- *We will take blood from your arm and a 24 hour urine sample, and examine them for different biological markers that may be present with infection and inflammation.*
- *We will monitor your heart with a portable machine called a Holter monitor for 24 hours*
- *We will take an ultra-sound of your heart to so we can look at the structure and function of your heart*

Who is undertaking the project?

This project is being conducted by Marie-Claire Seeley, Clinical Nurse Consultant at The Centre of Heart Rhythm Disorders and the Cardiovascular Centre, 62 Beulah Road in Norwood. This research will form the basis for the degree of PhD at the University of Adelaide under the supervision of Assoc/Prof Dennis Lau; who is a senior Cardiologists with expertise in heart rhythm disorders and POTS.

Why am I being invited to participate?

You are being invited because you belong to ONE of the groups below. Either:

You are being invited as you are a patient with POTS over the age of 18.

OR

You are being invited as you are a patient with Long Covid syndrome over the age of 18.

OR

You are being invited as you are a healthy adult over the age of 18.

What am I being invited to do?

You are being invited to participate in a study that will take two and a half hours at the Centre of Heart Rhythm Disorders site; Cardiovascular Centre, 62 Beulah Road, Norwood or the University of Adelaide Clinical Rooms, Nth Terrace, Adelaide. Or if you live in Melbourne, at *Cardio Vascular Services, 215 Kilby Road, Kew East, Victoria*.

In order to prepare you for the tests:

- You will be asked to abstain from coffee, tea, alcohol, caffeinated, high salt diet or energy drinks or chocolate (caffeine-free) for one day prior to the test and will be asked not to eat or drink for 8 hours prior to the test.
- Medications that could interact with the tests such as antiarrhythmic medication or blood pressure drugs will be withheld for at least 2 to 3 days prior to the test. The exact medications and doses to miss will be decided upon for you individually and will be reviewed by a senior clinician researcher. It is also desirable that your local doctor be advised of the decision to participate in this research project. You are encouraged to discuss the requirements for participation including medication withdrawal with this doctor.
- We will ask you to wear comfortable, loose clothing to your study appointment and to refrain from wearing any type of compression or abdominal support wear.
- We shall ask you some questions to ensure that you fit the study requirements and what your symptoms are in relation to your POTS/LCS; This information will be in the form of a questionnaire.
- Before you attend your study appointment, we will send you a link to an online questionnaire that will ask you questions about your health and how you function in daily life. These questions help us to determine how bad and how frequent certain symptoms are for you. The questionnaire can be stopped, saved and re-started so that you can complete it in stages rather than all at once.
- We will organize for you to have an Echocardiogram. This is a painless procedure where a technician uses a probe on the outside of your chest wall to record images of your heart and its blood flow via ultrasound. This helps to reassure us that you don't have any other heart condition that may be causing your symptoms before we commence the study.
- After your echocardiogram you will be given a heart rhythm monitor to wear for 24 hours and will be asked to return it the following day. This can be worn at home and with any activity (showering, dressing, with physical activity and at work. There will be no restrictions placed on your daily activities.
- After the study we will organize for you to undertake a 24 hour urine collection at home. We will give you some containers to catch all of your urine for 24hours and

then we will ask you to return these to the pathology unit that we nominate nearby. This test is painless but may be a little inconvenient as you will need to remain near to home in order to catch all your urine over this period.

On the testing day:

1. *We will take your blood pressure, temperature and heart rate and will measure your height and weight*
2. *We will use a machine to continually measure your blood pressure via a small cuff placed on your fingers and arm. While we are measuring your heart rate and blood pressure we will get you to undertake some breathing exercises as well as an exercise where you blow into a tube against pressure.*
3. *We will do an active standing test where we measure your heart rate and blood pressure while you are laying down and then we measure them every minute while you stand still for 10 minutes.*
4. *We will also test your sweat reflexes by getting you to stand with your bare hands and feet placed on a special plate connected to a machine. This generates an undetectable electrical pulse that stimulates your sweat glands. We can then measure your response to this.*
5. *We will get you to undertake around 30 minutes of concentration, memory and attention exercises on an IPAD. You can take breaks in between each exercise as you need.*
6. *We will take blood from your arm with a needle at the end of your assessment. We will fill three small vials which equals 15ml (or three teaspoons of blood).*

Otherwise you will be able to return home (and can drive immediately following the tests).

Future Research:

In addition, you will be given the opportunity to provide consent for 'unspecified' use of your data and blood samples once this research project is concluded. This allows the researchers to share your de-identified data with other researchers around the world. This information can then be used for other research projects related to Long Covid and POTS. We cannot predict what research projects they will be used for, however, none of your personal information that identifies you will be shared. Unspecified consent will also allow us to freeze and then use any of your remaining blood samples for future research. We cannot predict what this research might be, but it will be guided by appropriate human research practices, and institutional ethics will be granted before research commences.

You will not have to pay for any of the testing undertaken in this study and you will receive the results of these tests which may be of some benefit in the future. You will not be paid for participating in this study, however we recognise that financial hardship may be a barrier to travel and therefore participation in this study. Those who require financial assistance may discuss this further with researchers who can provide a travel stipend up to $30 on the production of receipts.

It is also desirable that your local doctor be advised of the decision to participate in this research project.

How much time will my involvement in the project take?

You will need to attend two study sessions. One will involve the 'pre-testing' where you will have your echocardiogram and the Holter monitor applied. There will also be one visit to the Cardiovascular Centre, 62 Beulah Road, Norwood, University of Adelaide Clinical Rooms, Nth Tce, Adelaide, or 215 Kilby Road, Kew East, Victoria that will last about 2.5 hours. We shall also request one brief visit (less than 5 minutes) to return equipment after a period of monitoring at home *the following day*. We would request the return of the equipment the *following day* and at a *maximum* of 48 hours from the date of the initial study so that we can use the monitor for other patients. Before the study you will need to do an online survey. This should take you around 40 minutes but for some people they may find it takes longer due to issues with concentration. You will be able to save your responses and log out of the survey and then log back in to complete it when you feel able.

Are there any risks associated with participating in this project?

Some participants will be required to stop medications such as those that control their heart rate before the study day. This is so the researchers can detect differences in how your heart reacts to different tests such as the deep breathing test. Stopping these medications is likely to allow some of your symptoms such as dizziness and fast heart rate, return. This is likely to be unpleasant for you and may take some days to recover once you restart your normal medication.
In general, all of these tests are fairly simple to perform and are very safe. Some monitoring equipment (pressure from the blood pressure cuff, sticky dots from the Holter monitor) and the blood test itself can cause some discomfort when the needle is placed on or through the skin.

In addition to the discomfort from the needle; there may be some discomfort from undertaking tests that may make you feel dizzy or unwell (such as the 10 minute standing test). We will have medical professionals present at all time and will stop the testing if you faint-although this is very unlikely even in POTS patients.

We would suggest that if possible, you have someone drive you to and from the testing if you are prone to 'dizziness' during these types of tests.

What are the potential benefits of the research project?

There will be no direct benefit to you from participating in this study. However, we will have greater knowledge of how POTS and LCS may be caused and how they impact on people's lives and health status. By participating in this study, you will contribute to the understanding of how our body's control of blood pressure changes and fluid volume with these disorders and whether different blood markers may potentially offer any future treatment strategies for all patients with your condition. You will receive the results from your echocardiogram, holter monitor and blood tests which may be of some benefit to you in terms of baseline health data for future comparison.

Can I withdraw from the project?

Participation in this project is completely voluntary. If you agree to participate, you can withdraw from the study at any time. If you withdraw after testing we will not be able to remove your data from analysis already undertaken, however any blood specimens will be destroyed to ensure they are no longer used in research. Electronic data pertaining to you will be permanently deleted from our study database. A decision not to participate will not affect your ongoing treatment in any way which is separate to this study.

What will happen to my information?

Confidentiality and privacy: All participants will have a code to identify them. This code will be used to de-identify your data. All of the data will be in the form of recordings of body vital signs, quality of life surveys as well as blood and urine markers. These details will be stored on one secured computer in

the University of Adelaide Centre for Heart Rhythm Disorders. Access to this computer will be restricted to study co-ordinators (listed below). While all efforts will be made to remove any information that might identify you, complete anonymity cannot be guaranteed. However, the utmost care will be taken to ensure that no personally identifying details are revealed.

Storage: All of your de-identified records from the experiments will be stored on one computer within the University of Adelaide secure database. Access to this information will be restricted to the study co-ordinators alone. The database is otherwise password protected and access is granted only to those researchers involved in the study. Any paper records (such as consent forms) will be housed under lock and key within the medical practice or the University of Adelaide, Centre for Heart Rhythm Disorders locked cabinets at the South Australian Health and Medical Research Institute (SAHMRI). They will be kept for up to 5 years. Electronic records will be stored for a maximum of 10 years. Your blood samples will be stored in locked, secure freezers at SAHMRI. A small portion of remaining blood will be kept and stored for future studies that involve POTS. These samples will be de-identified for this purpose.

Blood and Urine Storage:
Local Laboratory Samples: Some of the blood and all of your urine samples collected will be tested at a local laboratory. These samples will be labelled with your name and date of birth, as they would be if you were not in the research study. However, when the results from the testing of your samples are transferred to the study sponsor, they will not contain your name, only your study participant number. These samples will be securely destroyed after testing, according to the local laboratory's standard procedures.
Central Laboratory Samples: A small portion of your blood will be sent to a central University laboratory for processing. The central laboratory is located at the University of Adelaide. These samples will be labelled with your study participant number. The samples will not include your name or other information that could identify you. Your blood samples will be tested at this laboratory for specific markers of inflammation and antibodies that may relate to some of the symptom's POTS and post Covid patients experience. Remaining blood samples will be stored for additional testing depending on the trial outcomes, or for further scientific biomarker discovery for POTS and related diseases. It is not possible to predict all of the ways in which your blood might be used in the future, so it is not possible to tell you exactly how your sample will be used. However, this future research will require appropriate ethics approval from The University of Adelaide to ensure that researchers use your blood in an appropriate manner that complies with rules and regulations that govern human research practices. Only those associated with this study will have access to the coded data from the trial, data from the standardized and research tests, and information on the number, type and location of samples held, through a secure, password-protected database kept on a secure, password-protected server in a secure, restricted-access building.
Your remaining blood samples will be stored in locked, secure freezers in the University of Adelaide laboratory located at the South Australian Health and Medical Research Building. These samples will remain de-identified for this purpose. Samples utilised for the biomarkers indicated above will be managed, stored, tested and disposed of in accordance with good laboratory practice and applicable local regulations.

Publishing: The summary of data (medical conditions, age, gender as well as results from the tests) will be presented by way of posters, oral presentations, peer-reviewed medical journals and form part of a dissertation (thesis) to be presented to and examined by The University of Adelaide as a component of Marie-Claire's candidature for the degree of PhD. No individual data will be reported and none of your personal details will be identified.

Sharing: We may utilise the information gathered in this study to guide further experiments as well as utilise some of the data collected in future research projects. In all subsequent studies; summary data only will be used. Deidentified data is often shared through a secure database called 'Figshare' with other world researchers. This allows other scientists to understand and learn more about POTS. **None** of your identifiable information (such as contact details, name or DOB) will be shared in this manner.

Test Results: The purpose of this research is to explore links between different markers in your blood and

urine and to determine if these are common amongst those with POTS or LCS. We don't yet understand the significance of these markers and therefore it would not be beneficial to communicate the results to you or your treating doctor. However, some screening tests (such as routine blood measurements, Holter monitor and echocardiogram) may reveal findings that are useful for future comparison for your doctor. You will be provided with the option for the study team to notify your treating doctor of the results so that they may follow you up and provide appropriate medical care and advice in regard to the significance of these results. Some abnormal results may potentially reveal conditions that exclude you from further involvement in the study. This will be determined by the study investigators and communicated to you and your treating doctor. Withdrawal from the study will not interfere with your ongoing medical care which will continue to be provided by your nominated general practitioner.

Your information will only be used as described in this participant information sheet and it will only be disclosed according to the consent provided, except as required by law.

Who do I contact if I have questions about the project?

If you have any questions or would like further information about this study, or if you experience a research-related injury or illness, please contact Marie-Claire Seeley on (08) 8313 9000 (as the primary contact). Dr Dennis Lau or Dr Adrian Elliott on 08 8313 9000, or Dr Celine Gallagher on (08) 8222 2723.

What if I have a complaint or any concerns?

The study has been approved by the Human Research Ethics Committee at the University of Adelaide (approval number H-2021-xxx). This research project will be conducted according to the NHMRC National Statement on Ethical Conduct in Human Research (2007). If you have questions or problems associated with the practical aspects of your participation in the project, or wish to raise a concern or complaint about the project, then you should consult the Principal Investigator. If you wish to speak with an independent person regarding concerns or a complaint, the University's policy on research involving human participants, or your rights as a participant, please contact the Human Research Ethics

Committee's Secretariat on:
Phone: +61 8 8313 6028
Email: hrec@adelaide.edu.au
Post: Level 4, Rundle Mall Plaza, 50 Rundle Mall, ADELAIDE SA 5000
Any complaint or concern will be treated in confidence and fully investigated. You will be informed ofthe outcome.

If the study raises emotional concerns about your chronic health impacts, you may seek assistance from Beyond Blue on 1300 224636

If I want to participate, what do I do?

You are asked to contact Marie-Claire Seeley at POTS-LCS@sahmri.com to arrange a time to attend for the study and return the consent form (either by email, post or you can bring it with you on the day of the tests).

We thank you for taking the time to read this information sheet and should you decide to participate wethank you for your contribution.

Yours sincerely,

Marie-Claire Seeley, Dr Dennis Lau, Dr Adrian Elliott, Dr Celine Gallagher, Dr Tilenka Thynne, Erin

Attachment Two: Consent Form

Human Research Ethics Committee (HREC)

Title:	**Postural orthostatic tachycardia syndrome (POTS) in Long COVID syndrome: A detailed profiling study (POTS-LCS)**
Ethics Approval Number:	H-2021-053

CONSENT FORM

1. I have read the attached Information Sheet and agree to take part in the following research project:

2. I have had the project, so far as it affects me, and the potential risks and burdens fully explained to my satisfaction by the research worker. I have had the opportunity to ask any questions I may have about the project and my participation. My consent is given freely.

3. I have been given the opportunity to have a member of my family or a friend present while the project was explained to me.

4. Although I understand the purpose of the research project is to improve the quality of health/medical care, it has also been explained that my involvement may not be of any benefit to me.

5. I agree to participate in the activities as outlined in the participant information sheet.

6. I understand that as my participation is anonymous, I can withdraw any time and this will not affect medical advice in the management of my health, now or in the future. I am aware that Data already assigned analysed in this study prior to my request for removal cannot be retrieved by researchers who have already included it in analysis.

7. I have been informed that the information gained in the study may be published in a journal article, thesis, news article and/or conference presentations and I have been informed that in the published materials I will not be identified and my personal results will not be divulged.

8. I hereby provide consent for study investigators to share general pathology and diagnostic results which arise from this study, with the below named general practitioner (GP).

Yes ☐ No ☐

GP Name: _____ Fax:_____Ph:_____

Name of Medical Practice:_____

Address:_____

9. 'Unspecified Consent' is when a person gives consent for the future use of their data/samples and to be contacted again for other research projects. This means that data collected from this study can be made available world-wide in perpetuity for other researchers. However, no information that will identify you will be shared during this process.
   I hereby provide 'unspecified' consent for the use of my de-identified data in any future research:
   Yes ☐ No ☐

10. I understand my information will only be disclosed according to the consent provided, except where disclosure is required by law.

11. I am aware that I should keep a copy of this Consent Form, when completed, and the attached Information Sheet.

Participant to complete:

Name: _____ Signature: _____ Date:_____

Attachment 3: Introduction Email to POTS Clinic Patients

EMAIL OF INTRODUCTION

Date:

Dear _____,

You have been identified as a patient who has been diagnosed with Postural Orthostatic Tachycardia Syndrome (POTS). As you may be aware, POTS is a relatively underdiagnosed condition that may have significant impact on health outcomes for those who are affected by it. Associate Professor Dennis Lau and his supervised PhD student Marie-Claire Seeley are undertaking a study to explore the cardiovascular, immune and inflammatory profile of people with both POTS and Long Covid Syndrome (LCS). LCS is a syndrome that some people get after Covid-19 infection. In some people it seems to present with similar symptoms as POTS. We would like to understand if there are similarities in the blood, urine and cardiovascular profile of those with POTS and LCS. You have been identified as a person who may be eligible for inclusion in this study. Attached to this email you will find a patient information sheet and consent form that explains the purposes, risks and benefits of participation.. Please read this information and discuss further with your support persons or family members before deciding your involvement. You may contact Marie-Claire Seeley or any of the listed researchers for more information before making your decision.

Regards,

Assoc/Prof Dennis Lau
Marie-Claire Seeley
Dr Celine Gallagher
Dr Adrian Elliott
Dr Tilenka Thynne

The University of Adelaide, Centre for Heart Rhythm Disorders,
POTS-LCS@sahmri.com
Approval Number: H-2021-053

Attachment 4: Social Media Admin Email and Advert

Dear Social Media Administrators,

We are researchers at the University of Adelaide who are investigating the cardiovascular, immune and inflammatory profile of those with 'Long Covid'. We aim to compare results of blood tests and heart function with healthy controls as well as with people who have Postural Orthostatic Tachycardia Syndrome (POTS). Long Covid Syndrome is not yet well understood. We hope that this study will reveal underlying reasons for the extended fatigue, brain fog and cardiac and respiratory symptoms that these people suffer after Covid-19 infection. This study has ethics approval from The University of Adelaide H-2021-053

We would greatly appreciate your assistance in recruiting eligible study participants for this study by placing an advertisement in your social media support group. We understand that you may have questions in relation to the study that you would like to pose before making a decision. You are welcome to email us in return to discuss further. Below I have attached a copy of the advertisement we would like to place on your support page.

Regards,

Associate Professor Dennis Lau
Marie-Claire Seeley (PhD Student): POTS-LCS@sahmri.com
Dr Tilenka Thynne
Dr Celine Gallagher
Dr Adrian Elliot

LCS- Social Media Advert

Volunteers wanted for a study looking at the cardiovascular, immune and inflammatory function of those with "Long Covid Syndrome" and Postural Orthostatic Tachycardia Syndrome (POTS). Please contact Marie-Claire on POTS-LCS@sahmri.com for more details.

THE UNIVERSITY of ADELAIDE

This study involves 2 visits for cardiovascular testing either in Melbourne or Adelaide. These tests will take approximately 2-3 hrs and will also include blood and urine samples.

This study has ethics approval from The University of Adelaide, Human Research Ethics Committee H-2021-XXXX

Postural orthostatic tachycardia syndrome (POTS) in long COVID syndrome (LCS)

We are seeking male and female volunteers ≥18 years old to take part in a study investigating cardiac, kidney and immune function in 'Long Covid Syndrome' and Postural Orthostatic Tachycardia Syndrome (POTS). If you have had Covid-19 infection followed by >3 months of unexplained lingering symptoms, you may be eligible for this study.

If you are interested in this study you can contact Marie-Claire Seeley (Nurse Researcher) to discuss your eligibility at: POTS-LCS@sahmri.com

Attachment 5: University and SAHMRI Internet and Social Media Notice

Researchers from The University of Adelaide are looking for healthy volunteers for a study looking at cardiac function and blood markers in 'postural orthostatic tachycardia syndrome' and "Long Covid Syndrome". Please contact Marie-Claire on POTS-LCS@sahmri.com for more details.

THE UNIVERSITY of ADELAIDE

This study involves 2 visits for cardiovascular testing either in Melbourne or Adelaide. These tests will take approximately 2-3 hrs and will also include blood and urine samples.

This study has ethics approval from The University of Adelaide, Human Research Ethics Committee H-2021-xxxx

Postural orthostatic tachycardia syndrome (POTS) in long COVID syndrome (LCS)

We are seeking healthy male and female volunteers ≥18 years old to take part in a study investigating cardiac, kidney and immune function in 'Long Covid Syndrome' and Postural Orthostatic Tachycardia Syndrome (POTS). If you don't take medications and are healthy, you may be eligible for this study.

If you are interested in this study you can contact Marie-Claire Seeley (Nurse Researcher) to discuss your eligibility at: POTS-LCS@sahmri.com

Do You Have Postural Orthostatic Tachycardia Syndrome (POTS)?

The University of Adelaide, Centre for Heart Rhythm Disorders is looking for men and women to participate in a research study to evaluate the cardiovascular, immune and inflammatory causes of POTS and 'Long Covid'.

To qualify, participants in this study will be men and women who:

- Are 18 years or over
- Have been diagnosed with POTS by a medical doctor
- Additional requirements apply

Please email POTS-LCS@sahmri.com for more information and to find out if you are eligible to participate in the study.

Protocol POTS-LCS, V1, Recruitment Poster 1, 3rd April 2021, H-2021-053

THE UNIVERSITY of ADELAIDE

Are You a Healthy Adult Willing to Volunteer for a Study Exploring 'Long Covid'?

The University of Adelaide, Centre for Heart Rhythm Disorders are looking for men and women to participate in a research study to evaluate the cardiovascular, immune and inflammatory causes of 'Long Covid'.

To qualify, participants in this study will be men and women who:

- Are 18 years or over
- Have no other significant illnesses
- Do not take regular medication apart from the contraception pill

Please email POTS-LCS@sahmri.com for more information and to find out if you are eligible to participate in the study.

Protocol POTS-LCS, V1, Recruitment Poster 1, 21st March 2021, H-2021-053

National Statement on Ethical Conduct in Human Research

Biospecimen Research

Project title: Postural orthostatic tachycardia syndrome (POTS) in Long COVID syndrome: A detailed profiling study (POTS-LCS)

Application ID: HREC 2021: 35073

Principal Investigator: Assoc/Prof Dennis Lau

Chapter 3.2 Human biospecimens in laboratory based research

Element 1: Research Scope, aims, themes, questions, and methods

Prospective collection of human biospecimens for research (section 3.2.1):
[The secondary aim of this study is to Characterise the neuroendocrine/inflammatory/immune biomarker profile of those with LCS(+)POTS/LCS(-)POTS and POTS and compare to matched, healthy controls. As such the prospective collection of human blood and urine relates directly to the stated objectives of the study.]

Use of stored human biospecimens for research (section 3.2.2):
[This study will not use previously stored biospecimens for its purposes. However, consent will be sort from participants to store a small sample of blood post completion of the study. Specific consent will be sort for this in the Patient Information and Consent Sheet. The purpose of this relates to the embryonic understanding of the neuro-endocrine, inflammatory and immune involvement in POTS and LCS. It is foreseeable that emerging understanding of these conditions may elucidate contributing pathophysiology. Stored samples from these cohorts could allow for further studies to be undertaken without the added burden of additional blood draw. Stored samples would not be utilised for such purposes without appropriate ethics approval.]

Use of only stored biospecimens with no more than low risk (section 3.2.3)
[Not relevant to this study.]

Element 2: Recruitment

Prospective collection of human biospecimens for research (section 3.2.4):

Burden justified by potential benefits: [Type response here]

(a) **Burden justified by potential benefits:** [The burdens of the blood collection on the donor(s) are justified by the potential benefits of this proposed research. POTS and LCS have a significant patient burden in terms of reduced quality of life and high community and health care burden. This study has the potential to elucidate biomarkers that inform understanding of disease aetiology, diagnosis and treatment which may in turn lead to mitigation of these burdens.]

(b) **Suitable qualification and experience of those involved in collection:** [Blood collection will be undertaken via a qualified and registered pathology collection service as well as by clinically trained and qualified researchers. These researchers include medical doctors and registered nurses who are experienced in the practices of safe blood collection and will adhere to best practice guidelines for phlebotomy. All blood collection with be undertaken in an appropriate clinical setting.]

(c) **Arrangements for intended processing, storage, distribution and/or use, and disposal of biospecimens:** [Blood specimens will be deidentified, spun in a centrifuge and frozen and stored in locked bio-secure freezers at the South Australian Health and Medical Research Institute to facilitate analysis.

Routine blood samples will be processed in accordance with current guidelines as detailed by the associated, accredited pathology group. Blood samples will be deidentified and coded before being sent to the pathology provider. Not participant details will be shared with third party providers.

Blood sample analysis undertaken by the researchers are detailed below. The principal investigator will be responsible for the permanent and safe disposal of samples as per University of Adelaide policies that govern safe handling of bio-specimens.

- ELISA kits to detect autoantibodies against the α1 adrenergic b-1 adrenergic, M1 receptors and M4 muscarinic cholinergic receptor antibodies will be purchased form CellTrend GmbH (Luckenwalde, Germany). Samples will be processed as per the manufacturer's instruction
- Inflammatory biomarkers will be processed using ProcartaPlex™ Multiplex Immunoassay as per manufacturer's instructions.
- Copeptin: Morning blood test with a 8 hr food fast (drink to thirst). Plasma will be collected in EDTA tubes, centrifuged and kept in -80 degrees freezer before batch analysis using the Thermo Scientific B·R·A·H·M·S Copeptin proAVP KRYPTOR assay using B·R·A·H·M·S KRYPTOR compact PLUS, Hennigsdorf, Germany). All data will be deidentified and stored as per above procedures

Human biospecimens obtained After death for research (section 3.2.5)

[Not applicable to this study]

Use of human biospecimens collected for clinical purposes (section 3.2.6)

[~~Human biospecimens that have been obtained for clinical purposes and have been retained by an accredited clinical pathology service may be utilised in this study. The identity of the donor is not necessary for this activity and samples will be de-identified for this purpose.~~ Not applicable to this study]

Importation and exportation of human biospecimens for research (section 3.2.7 – 3.2.9)

[There is no intention to export or import human biospecimens for this study.

Transitioning provisions for existing biospecimens (section 3.2.10)

[Not applicable as the biospecimens for this study will not be obtained before December 2013]

Element 3: Consent

Prospective collection of human biospecimens for research (sections 3.2.11, 3.2.12):

Consent forms for donors will be obtained and recorded (3.2.11)

Information given to participants before obtaining consent is (section 3.2.12):

(a) research for which the biospecimens are to be used;
(b) how specimens will be stored, used and disposed of including processes to respect their personal or cultural sensitivities;
(c) extent to which the biospecimens will be reasonably identifiable and how privacy and confidentiality will be respected;
(d) whether the research is likely to provide information that may be important to their health or to the health of their relatives or their community;
(e) if (d) applies, whether or not they will have the choice to receive this information and how this will be managed;
(f) if (d) applies, whether or not they will have the choice for it to be provided to their relatives or to their community and how this will be managed;
(g) whether the biospecimens and associated data may be distributed to other researchers, including those outside Australia;
(h) right to withdraw consent for continued use of their biospecimens or associated data and any limitations that may be relevant;
(i) financial or personal interests that those engaged in the collection, processing storage and distribution and use of their biospecimens may have; and
(j) any potential for commercial application of any outcomes of the research.

(a): The Patient Information Sheet contains information that informs the participants of why the biospecimens are important to the research. Unspecified consent and future use of blood samples are described and requested in the patient consent form.

(b): Plasma will be collected in EDTA tubes, centrifuged and kept in -80 degrees freezer at the locked University of Adelaide Laboratory, Level 6 laboratory, SAHMRI, before batch analysis. The principal investigator will oversee appropriate destruction of samples in accordance with University and Laboratory protocols that detail the safe and respectful disposal of human biospecimens. The date, time and method of destruction of the samples will be recorded in the lab archives and stored for a minimum of 10 years on the University encrypted, electronic platform. The specimens will only be used in the manner to which consent was granted for their use.

(c): Participant medical information will be stored electronically on an encrypted server within the Centre for Heart Rhythm Disorders. Identifiable information such as names, birthdates, contact details, and medical record numbers will not be stored with biospecimens but rather will be replaced with a linkage code. Access to participant medical information contained within the database will be restricted to CHRD investigators named on this protocol.

Information linking the linkage codes to the participants' identifiable information will be stored in a secure location separate from the biospecimen. Access to the information linking the linkage codes with information that may identify participants will be granted only to CHRD investigators named on this protocol on a need-to-know basis as approved by the Principal Investigator of POTS-LCS. Access to the information linking the linkage codes with participant identifiers shall be documented.

Blood samples will be stored by the principal investigator in the University of Adelaide CHRD locked laboratory at the South Australian Health and Medical Research Building, and recorded in the University's metadata store. All access to said samples will be approved by the Principal Investigator and logged in the study logbooks.

(d): Use of biospecimens in this study are predominantly exploratory. Results of testing of inflammatory/immune markers will not be able to be deemed of clinical significance due to lack of current understanding of these conditions. Therefore, the outcomes of these biospecimen analysis would not result in information about a participant's future health ~~or risk of having children with a genetic disorder,~~ or information that may be relevant to the health of family members who are not part of the trial. However, routine blood and urine tests may indicate 'out of range' results that could be of significance to current health and therefore will be shared (with consent) to the participants nominated general practitioner.

(e): ~~Not applicable~~Participants will have the choice to nominate and consent for results to be shared with their treating general practitioner

(f): ~~Not applicable~~These results will not be relevant to family or community as they pertain to routine blood and urine results and not to gene or other markers that may affect communities or families.

(g): Associated data from the analysis of biospecimens will be uploaded to 'figshare' for international collaborative research use. No identifiable information will be shared. Remaining biospecimens will be stored for future use from the same research group. The patient consent form asks for consent for the same and other researchers to use remaining samples for future research. There is no intention or request of participants for use of their samples for exportation.

(h): Traceability of the blood samples and data will remain possible in order to enable participant withdrawal. On application of withdrawal participant's biospecimens will be destroyed as per University of Adelaide protocols pertaining to the safe handling and destruction of human tissue. Where samples have already been included in research analysis it will not be possible to withdraw this data. This is detailed in the PICF. However remaining specimens will be destroyed in a manner that allows for sensitivity to cultural and religious practices as requested by individuals and their respective communities.

(i): The researchers have no other relevant financial interests pertaining to the collection, storage and use of the biospecimens.

(j): There are no foreseeable commercial applications of any of the outcomes of this research involving collection of biospecimens.

Use of stored human biospecimens for research (section 3.12.13 – 3.12.14)

[The blood specimens in this study will only be used in the manner detailed on the patient consent form. Samples will be de-identified and replaced with a traceable code. This will allow for re-contact of the donor for future consent of use of their biospecimen in research.]

Element 5: Communication of research findings or results to participants (section 3.2.15):

Where proposed research involving use of human biospecimens may be important for the health of the donors, their relatives or their community, researchers should prepare an ethically defensible plan to describe management of any proposed disclosure or non-disclosure of that information including the elements in (a) – (i).

[As per element d) above. The results of biospecimen analysis in this study do not pertain to genetic or other information that would be deemed relevant and important information for the health of the donor and/or their family and community. As such there is no plan for communication of the analysis

results to the individual, family or community. However results from routine blood and urine samples undertaken in this study may be deemed clinically significant for current or future comparison and therefore copies of the results of these will be forwarded to participants nominated general practitioner. Consent for sharing of this information will be included in the consent form.]

36- Item Short Form Survey Instrument (SF-36)

RAND 36-Item Health Survey 1.0 Questionnaire Items

Choose one option for each questionnaire item.

1. In general, would you say your health is:

- 1 - Excellent
- 2 - Very good
- 3 - Good
- 4 - Fair
- 5 - Poor

---

2. **Compared to one year ago**, how would you rate your health in general **now**?

- 1 - Much better now than one year ago
- 2 - Somewhat better now than one year ago
- 3 - About the same
- 4 - Somewhat worse now than one year ago
- 5 - Much worse now than one year ago

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	○ 1	○ 2	○ 3
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○ 1	○ 2	○ 3
5. Lifting or carrying groceries	○ 1	○ 2	○ 3
6. Climbing **several** flights of stairs	○ 1	○ 2	○ 3
7. Climbing **one** flight of stairs	○ 1	○ 2	○ 3
8. Bending, kneeling, or stooping	○ 1	○ 2	○ 3
9. Walking **more than a mile**	○ 1	○ 2	○ 3
10. Walking **several blocks**	○ 1	○ 2	○ 3
11. Walking **one block**	○ 1	○ 2	○ 3
12. Bathing or dressing yourself	○ 1	○ 2	○ 3

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	Yes	No
13. Cut down the **amount of time** you spent on work or other activities	1	2
14. **Accomplished less** than you would like	1	2
15. Were limited in the **kind** of work or other activities	1	2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	1	2
18. **Accomplished less** than you would like	1	2
19. Didn't do work or other activities as **carefully** as usual	1	2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- 1 - Not at all
- 2 - Slightly
- 3 - Moderately
- 4 - Quite a bit
- 5 - Extremely

21. How much **bodily** pain have you had during the **past 4 weeks**?

- 1 - None
- 2 - Very mild
- 3 - Mild
- 4 - Moderate
- 5 - Severe
- 6 - Very severe

---

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

- 1 - Not at all
- 2 - A little bit
- 3 - Moderately
- 4 - Quite a bit
- 5 - Extremely

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

32. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

- 1 - All of the time
- 2 - Most of the time
- 3 - Some of the time
- 4 - A little of the time
- 5 - None of the time

How TRUE or FALSE is **each** of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5

ABOUT

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Santa Monica, California 90401-3208

EQ-5D-5L

Health Questionnaire

English version for Australia

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems with walking around ❑
I have slight problems with walking around ❑
I have moderate problems with walking around ❑
I have severe problems with walking around ❑
I am unable to walk around ❑

PERSONAL CARE

I have no problems with washing or dressing myself ❑
I have slight problems with washing or dressing myself ❑
I have moderate problems with washing or dressing myself ❑
I have severe problems with washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

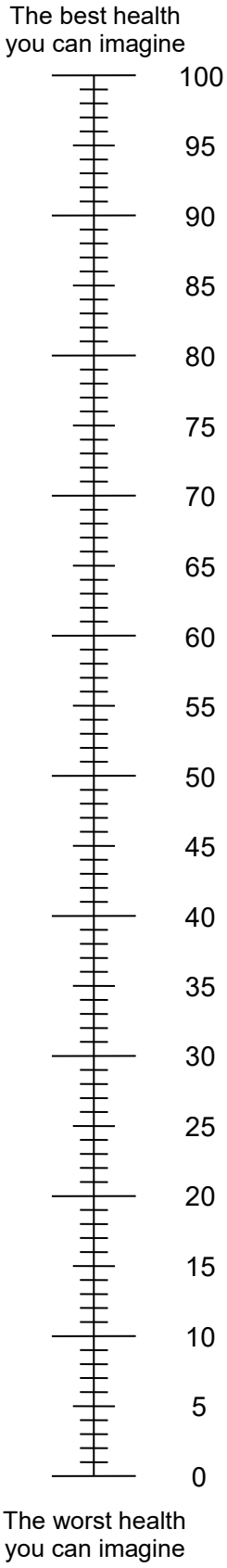
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Supplemental Appendix 2. Instrument - COMPASS 31

1. In the past year, have you ever felt faint, dizzy, “goofy”, or had difficulty thinking soon after standing up from a sitting or lying position?

1 Yes
2 No (if you marked No, please skip to question 5)

2. When standing up, how frequently do you get these feelings or symptoms?

1 Rarely
2 Occasionally
3 Frequently
4 Almost Always

3. How would you rate the severity of these feelings or symptoms?

1 Mild
2 Moderate
3 Severe

4. In the past year, have these feelings or symptoms that you have experienced:

1 Gotten much worse
2 Gotten somewhat worse
3 Stayed about the same
4 Gotten somewhat better
5 Gotten much better
6 Completely gone

5. In the past year, have you ever noticed color changes in your skin, such as red, white, or purple?

1 Yes
2 No (if you marked No, please skip to question 8)

6. What parts of your body are affected by these color changes? (Check all that apply)

1 Hands
2 Feet

7. Are these changes in your skin color:

1 Getting much worse
2 Getting somewhat worse
3 Staying about the same
4 Getting somewhat better
5 Getting much better
6 Completely gone

8. In the past 5 years, what changes, if any, have occurred in your general body sweating?

1 I sweat much more than I used to
2 I sweat somewhat more than I used to
3 I haven't noticed any changes in my sweating
4 I sweat somewhat less than I used to
5 I sweat much less than I used to

9. Do your eyes feel excessively dry?

1 Yes
2 No

10. Does you mouth feel excessively dry?

1 Yes
2 No

11. For the symptom of dry eyes or dry mouth that you have had for the longest period of time, is this symptom:

1 I have not had any of these symptoms
2 Getting much worse
3 Getting somewhat worse
4 Staying about the same
5 Getting somewhat better
6 Getting much better
7 Completely gone

12. In the past year, have you noticed any changes in how quickly you get full when eating a meal?

1 I get full a lot more quickly now than I used to
2 I get full more quickly now than I used to
3 I haven't noticed any change
4 I get full less quickly now than I used to
5 I get full a lot less quickly now than I used to

13. In the past year, have you felt excessively full or persistently full (bloated feeling) after a meal?

1 Never
2 Sometimes
3 A lot of the time

14. In the past year, have you vomited after a meal?

1 Never
2 Sometimes
3 A lot of the time

15. In the past year, have you had a cramping or colicky abdominal pain?
    1 Never
    2 Sometimes
    3 A lot of the time

16. In the past year, have you had any bouts of diarrhea?
    1 Yes
    2 No (if you marked No, please skip to question 20)

17. How frequently does this occur?
    1 Rarely
    2 Occasionally
    3 Frequently _____ times per month
    4 Constantly

18. How severe are these bouts of diarrhea?
    1 Mild
    2 Moderate
    3 Severe

19. Are your bouts of diarrhea getting:
    1 Much worse
    2 Somewhat worse
    3 Staying the same
    4 Somewhat better
    5 Much better
    6 Completely gone

20. In the past year, have you been constipated?
    1 Yes
    2 No (if you marked No, please skip to question 24)

21. How frequently are you constipated?
    1 Rarely
    2 Occasionally
    3 Frequently _____ times per month
    4 Constantly

22. How severe are these episodes of constipation?
    1 Mild
    2 Moderate
    3 Severe

23. Is your constipation getting:

1 Much worse
2 Somewhat worse
3 Staying the same
4 Somewhat better
5 Much better
6 Completely gone

24. In the past year, have you ever lost control of your bladder function?

1 Never
2 Occasionally
3 Frequently _____ times per month
4 Constantly

25. In the past year, have you had difficulty passing urine?

1 Never
2 Occasionally
3 Frequently _____ times per month
4 Constantly

26. In the past year, have you had trouble completely emptying your bladder?

1 Never
2 Occasionally
3 Frequently _____ times per month
4 Constantly

27. In the past year, without sunglasses or tinted glasses, has bright light bothered your eyes?

1 Never (if you marked Never, please skip to question 29)
2 Occasionally
3 Frequently
4 Constantly

28. How severe is this sensitivity to bright light?

1 Mild
2 Moderate
3 Severe

29. In the past year, have you had trouble focusing your eyes?

1 Never (if you marked Never, please skip to question 31)
2 Occasionally
3 Frequently
4 Constantly

30. How severe is this focusing problem?

1 Mild
2 Moderate
3 Severe

31. Is the most troublesome symptom with your eyes (i.e. sensitivity to bright light or trouble focusing) getting:

1 I have not had any of these symptoms
2 Much worse
3 Somewhat worse
4 Staying about the same
5 Somewhat better
6 Much better
7 Completely gone

FATIGUE SEVERITY SCALE (FSS)

Date _____ Name _____

Please circle the number between 1 and 7 which you feel best fits the following statements. This refers to your usual way of life within the last week. 1 indicates "strongly disagree" and 7 indicates "strongly agree."

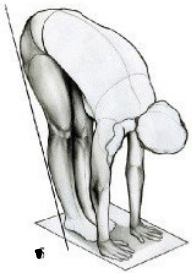
Read and circle a number.	Strongly Disagree → Strongly Agree						
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

VISUAL ANALOGUE FATIGUE SCALE (VAFS)

Please mark an "X" on the number line which describes your global fatigue with 0 being worst and 10 being normal.

0	1	2	3	4	5	6	7	8	9	10

1. Can you now (or could you ever) place your hands flat on the floor without bending knees?



   Yes ☐

   No ☐

2. Can you now (or could you ever) bend your thumb to touch your forearm?

   Yes ☐

   No ☐

3. As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?

   Yes ☐

   No ☐

4. As a child or teenager, did your kneecap, elbow or shoulder dislocate on more than one occasion?

   Yes ☐

   No ☐

   Please give details including joint: _____

5. Do you consider yourself “double-jointed”?

   Yes ☐

   No ☐

Office Use:
Score: _____

Folci, M., & Capsoni, F. (2016). *17*. doi:10.1186/s12891-016-0905-2

ORTHOSTATIC HYPOTENSION QUESTIONNAIRE (OHQ)

Patient Instructions: We are interested in measuring the symptoms that occur because of your problem with low blood pressure (orthostatic hypotension) and the degree that those symptoms may interfere with your daily activity. It is important that we measure the symptoms that are due ONLY to your low blood pressure, and not something else (like diabetes or Parkinson's disease). Many people know which of their symptoms are due to low blood pressure. Some people who have recently developed problems with low blood pressure may not easily distinguish symptoms of low blood pressure from symptoms caused by other conditions. In general, symptoms of your low blood pressure problem will appear either upon standing or after you have been standing for some time, and will usually improve if you sit down or lie down. Some patients even have symptoms when they are sitting which might improve after lying down. Some people have symptoms that improve only after sitting or lying down for quite some time.

Please answer the questions below keeping in mind that we want to know only about those symptoms that are from your problem with low blood pressure.

OH SYMPTOM ASSESSMENT (OHSA)

Please tick the number on the scale that best rates how severe your symptoms from low blood pressure have been on the average over the past week. You should respond to every symptom. If you do not experience the symptom, circle zero (0). YOU SHOULD RATE ONLY THE SYMPTOMS THAT ARE DUE TO YOUR LOW BLOOD PRESSURE PROBLEM.

None	**1. Dizziness, lightheadedness, feeling faint, or feeling like you might black out**										Worst possible
	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
None	**2. Problems with vision (blurring, seeing spots, tunnel vision, etc.)**										Worst possible
	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
None	**3. Weakness**										Worst possible
	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
None	**4. Fatigue**										Worst possible
	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
None	**5. Trouble concentrating**										Worst possible
	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
None	**6. Head and neck discomfort**										Worst possible
	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

OH DAILY ACTIVITY SCALE (OHDAS)

We are interested in how the low blood pressure symptoms that you experiences affect daily life. Please rate each item by ticking the number that best represents how much on the average the activity has been interfered with over the past week by the low blood pressure symptoms you have experienced. If you cannot do the activity for reasons other than low blood pressure, please check the box at right.

No interference	**1. Activities that require standing for a short time**							☐ Cannot do for other reasons				Total interference
	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	
No interference	**2. Activities that require standing for a long time**							☐ Cannot do for other reasons				Total interference
	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	
No interference	**3. Activities that require walking for a short time**							☐ Cannot do for other reasons				Total interference
	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	
No interference	**4. Activities that require walking for a long time**							☐ Cannot do for other reasons				Total interference
	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	

Supplementary Material #1

The Gastroparesis Cardinal Symptom Index (GCSI)

GCSI score will be calculated as per Revicki 2004 (1):

Response scale

(0) None
(1) Very mild
(2) Mild
(3) Moderate
(4) Severe
(5) Very severe

Items

Please rate the severity of the following symptoms during the past 2 weeks:

1. Nausea
2. Retching (heaving as if to vomit, but nothing comes up)
3. Vomiting
4. Stomach fullness
5. Not able to finish a normal-sized meal
6. Feeling excessively full after meals
7. Loss of appetite
8. Bloating (feeling like you need to loosen your clothes)
9. Stomach or belly visibly larger

Calculation of GCSI-score

1. Nausea/vomiting-score: Average score of items 1-3
2. Early satiety-score: Average score of items 4-7
3. Bloating-score: Average score of items 8-9
4. GCSI-score: Average of all three sub-scores

References:

1. Revicki DA, Rentz AM, Dubois D, Kahrilas P, Stanghellini V, Talley NJ, et al. Gastroparesis Cardinal Symptom Index (GCSI): development and validation of a patient reported assessment of severity of gastroparesis symptoms. Qual Life Res. 2004 May;13(4):833–44.

Reaction Time (RTI)

Reaction Time provides assessments of motor and mental response speeds, as well as measures of movement time, reaction time, response accuracy and impulsivity.

Administration time

3 minutes

Task format

The participant must select and hold a button at the bottom of the screen. Circles are presented above (one for the simple mode, and five for the five-choice mode.) In each case, a yellow dot will appear in one of the circles, and the participant must react as soon as possible, releasing the button at the bottom of the screen, and selecting the circle in which the dot appeared.

Outcome measures

Outcome measures are divided into reaction time and movement time for both the simple and five-choice variants.

Normative data

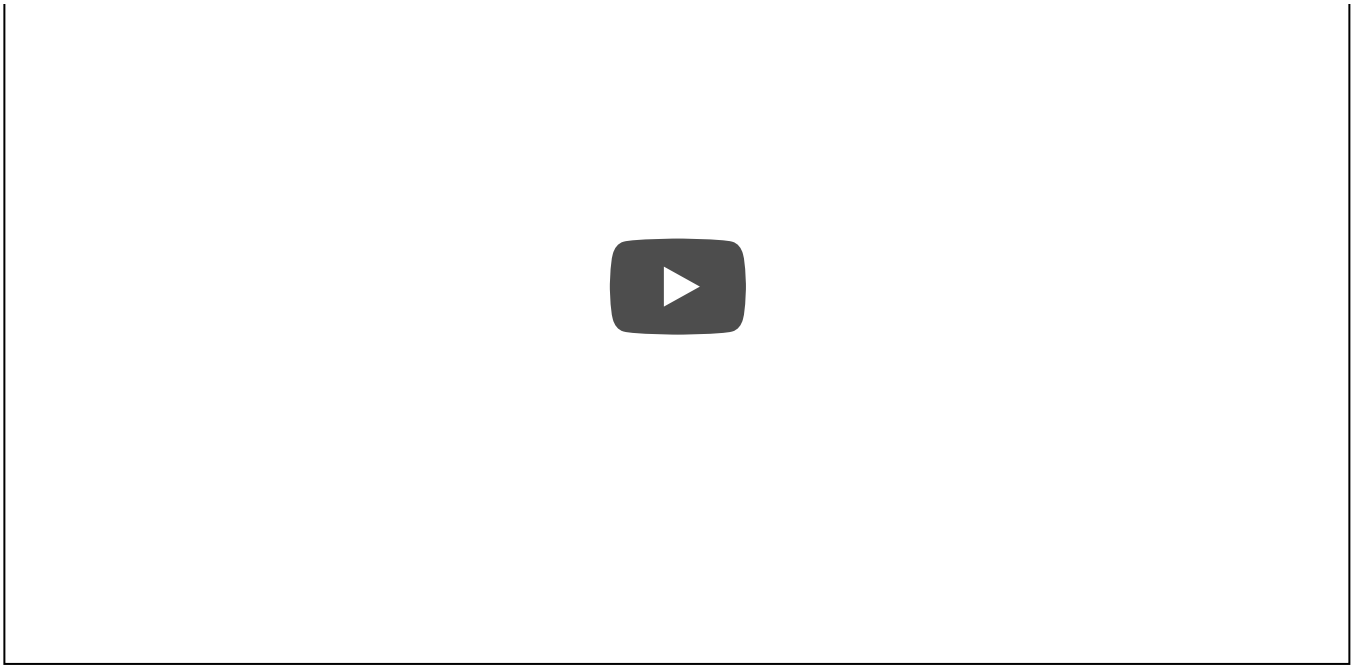
Please contact us to discuss your normative data requirements. Please note, we do not recommend using normative data in place of a control group.

When to use this test

We would recommend using this test to assess cognitive function in:

- Autism spectrum disorder
- Alzheimer's disease
- Epilepsy
- Schizophrenia
- Multiple sclerosis
- Stroke and cerebrovascular disease
- Parkinson's disease
- Huntington's disease
- Traumatic brain injury
- Down's syndrome

CANTAB Reaction Time



MOTOR SCREENING TASK (MOT)

RAPID VISUAL INFORMATION PROCESSING (RVP)

REACTION TIME (RTI)

MATCH TO SAMPLE VISUAL SEARCH (MTS)

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Rapid Visual Information Processing (RVP)

Rapid Visual Information Processing is a measure of sustained attention.

Administration time

7 minutes

Task format

A white box is shown in the centre of the screen, inside which digits from 2 to 9 appear in a pseudo-random order, at the rate of 100 digits per minute. Participants are requested to detect target sequences of digits (for example, 2-4-6, 3-5-7, 4-6-8). When the participant sees the target sequence they must respond by selecting the button in the centre of the screen as quickly as possible. The level of difficulty varies with either one- or three-target sequences that the participant must watch for at the same time.

Outcome measures

Outcome measures cover latency (speed of response), probability of false alarms and sensitivity.

Normative data

Please contact us to discuss your normative data requirements. Please note, we do not recommend using normative data in place of a control group.

When to use this test

We would recommend using this test to assess cognitive function in:

- Alzheimer's disease
- Depression and affective disorders
- Epilepsy
- Multiple sclerosis
- Neuromuscular disease
- Schizophrenia

CANTAB Rapid Visual Information Processing

MOTOR SCREENING TASK (MOT)

RAPID VISUAL INFORMATION PROCESSING (RVP)

REACTION TIME (RTI)

MATCH TO SAMPLE VISUAL SEARCH (MTS)

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Multitasking Test (MTT)

The Multitasking Test is a test of the participant's ability to manage conflicting information provided by the direction of an arrow and its location on the screen and to ignore task-irrelevant information.

Administration time

8 minutes

Task format

The test displays an arrow which can appear on either side of the screen (right or left) and can point in either direction (to the right or to the left).

Each trial displays a cue at the top of the screen that indicates to the participant whether they have to select the right or left button according to the "side on which the arrow appeared" or the "direction in which the arrow was pointing".

In some sections of the task this rule is consistent across trials (single task) while in others it may change from trial to trial in a randomised order (multitasking). Using both rules in a flexible manner places a higher demand on cognition than using a single rule.

Some trials display congruent stimuli (e.g. arrow on the right side pointing to the right) whereas other trials display incongruent stimuli, which require a higher cognitive demand (e.g. arrow on the right side of the screen pointing to the left).

Outcome measures

Outcome measures for the Multitasking Test include response latencies and error scores that reflect the participant's ability to manage multitasking and the interference of incongruent task-irrelevant information on task performance (i.e. a Stroop-like effect).

Normative data

Please contact us to discuss your normative data requirements. Please note, we do not recommend using normative data in place of a control group.

When to use this test

We would recommend using this test to assess cognitive function in:

- Traumatic brain injury

- Autism
- Down's syndrome

CAMBRIDGE GAMBLING TASK (CGT)

INTRA-EXTRA DIMENSIONAL SET SHIFT (IED)

MULTITASKING TEST (MTT)

ONE TOUCH STOCKINGS OF CAMBRIDGE (OTS)

STOCKINGS OF CAMBRIDGE (SOC)

SPATIAL WORKING MEMORY (SWM)

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Delayed Matching to Sample (DMS)

Delayed Matching to Sample assesses both simultaneous visual matching ability and short-term visual recognition memory, for non-verbalisable patterns.

Administration time

7 minutes

Task format

The participant is shown a complex visual pattern, that is both abstract and non-verbal (the sample), followed by four similar patterns, after a brief delay. The participant must select the pattern which exactly matches the sample. In some trials the sample and the choice patterns are shown simultaneously, in others there is a delay (of 0, 4 or 12 seconds) before the four choices appear.

Outcome measures

Outcome measures include latency (the participant's speed of response), the number of correct patterns selected and a statistical measure giving the probability of an error after a correct or incorrect response.

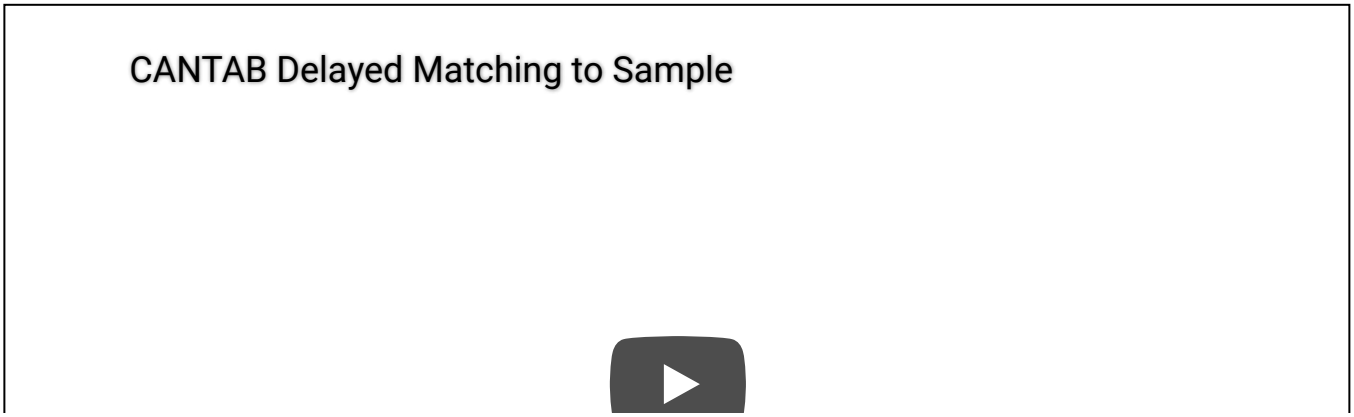
Normative data

Please contact us to discuss your normative data requirements. Please note, we do not recommend using normative data in place of a control group.

When to use this test

We would recommend using this test to assess cognitive function in:

- Alzheimer's disease (mild to moderate and prodromal)
- Depression and affective disorders



DELAYED MATCHING TO SAMPLE (DMS)

PAIRED ASSOCIATES LEARNING (PAL)

PATTERN RECOGNITION MEMORY (PRM)

VERBAL RECOGNITION MEMORY (VRM)

STOP SIGNAL TASK (SST)

SPATIAL SPAN (SSP)

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