UQ Strategic Funding Annual/Final Report

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SECTION 1: ADMINISTRATIVE SUMMARY

If this an Annual or a Final Report?	Annual	2023
VC/DVCR Commitment ID (if known):	VCSF200001A DVCR19300A	
Project Title:	Queensland Cystic Fibrosis Research Program (QCFRP)	
Lead CI / Funding Recipient Name:	Prof Peter D Sly	
Administering School/Centre:	CHRC	
Faculty/Institute:	Medicine	
Years of Funding Requested (YYYY - YYYY):	2020-2024	

SECTION 2: OBJECTIVES

Note: Dot points are acceptable for the items below

UQ's Child Health Research Centre (CHRC) hosts two internationally recognised research leaders in Cystic Fibrosis (CF), Professors Peter Sly and Claire Wainwright. They work in close collaboration with Professor Scott Bell. Their work has resulted in > 300 publications in this field and improved clinical treatment for children with CF around the world.
In recognition of their work, they were invited by the American Cystic Fibrosis Foundation (CFF) to apply for special 'out of round' funding. This was successful with more than $7.5 million (USD) awarded, across three awards, one fronted by each researcher.

This funding request is to leverage funds ($2.5 million AUD) committed by the Qld Children's Hospital Foundation (CHF) in support of this program. This will enable expansion of the project and ensure timely completion. Most importantly, it will enable the team to deliver better outcomes for patients with CF.

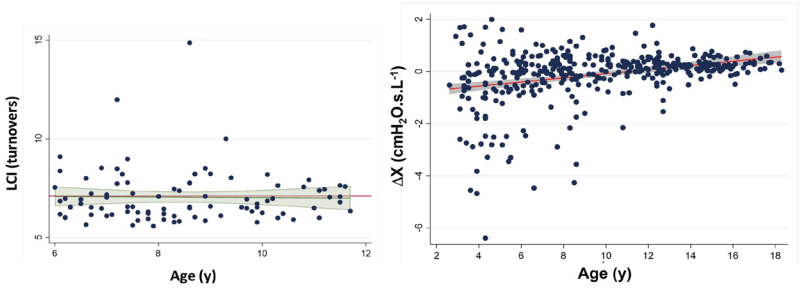
SECTION 3: STATEMENT OF PROGRESS/OUTCOMES

ELO recruitment and study visits
The Queensland Children's Hospital (**QCH**) has the largest CF clinic in the Southern Hemisphere, caring for >470 children with CF. Of these, ~360 are routinely seen at QCH clinics, with 196 being recruited into ELO. In addition, 42 adults have been recruited from TPCH and 28 from the Mater hospital. Data have been collected from 296 annual reviews and 765 clinic visits.

Lung function trajectories: ELO raw data show a surprising improvement in lung function with increasing age (Fig. 1); both LCI and ΔX trend towards normal in older children. This is likely to be an effect of ETI therapy as this is not seen in younger children. Median (25%,75%) LCI in the ELO cohort ≥12y (number of assessments=49) was 6.68 (6.18, 7.80) TO; for 6-11y olds (n=91) the median was

6.71 (6.2, 7.58) TO and for <6y (n=57) the median was 7.59 (6.86, 7.59) TO. A similar pattern is seen with volume dependance of reactance (**ΔX)** (Fig. 1); cohort ≥12y (n=122) was 0.23 (0.06, 0.37) $cmH_2O.s.L^{-1}$, 6-11y(n=161) 0.92 (-0.26, 0.40) $cmH_2O.s.L^{-1}$, and <6y (n=92) -0.69 (-1.18, 0.16) $cmH_2O.s.L^{-1}$). *These data illustrate a) the strength of our existing baseline data to provide objective real-world evidence on changes in peripheral airway function when transitioning onto ETI and b) our ability to provide data to support the need for ETI in <6y olds.*

Fig 1: Lung function vs Age in the ELO cohort. Line of best fit and confidence limits shown



Urinary GSA as a clinical biomarker of neutrophil-induced oxidative stress.

We have shown that exaggerated neutrophilic inflammation and neutrophil-induced OS are major drivers of early and progressive CF lung disease. Increasing levels of GSA in bronchoalveolar lavage (**BAL**) correlate with *P. aeruginosa* infections and radiological bronchiectasis in people with CF (pwCF). In addition, GSA measured in the urine correlated well with GSA levels in BAL and other markers of neutrophilic inflammation (allantoin, IL-1B and IL-6). These data suggest a role for urinary GSA as a non-invasive biomarker capable of identifying and tracking inflammatory disease activity in pwCF. To address this question, we followed 102 ELO children (median age 11.5y, 25%-75% 6.4-14.4y) who were admitted to hospital for management of APEx and/or eradication of *P. aeruginosa, S. aureus,* or *Aspergillus*. All participants reported an increase in wet cough and/or sputum production at the time of their admission. 122 admissions occurred during the study period with 145 samples collected: 87 on day 1 of admission and 58 on day of discharge. The mean length of admission was 14 days (SD 4, range 7-39 days). When analyzing all samples, a statistically significant difference was observed between samples collected at admission vs. discharge for children (0.14 [0.07-0.21] µM vs. 0.10 [0.06-0.22] µM, p=0.034). Matched admission-discharge samples were available for 49 children. A statistically significant difference was observed between admission and discharge results (0.15 [0.07-0.20] µM vs. 0.09 [0.06-0.14] µM, p=0.024). Thirty-four participants (69.3%) had lower GSA levels at discharge (compared to admission), while 15 participants (30.6%) had an increase in GSA results at discharge. Weak positive correlations existed between GSA on admission and age (rho=0.113, p=0.04), sex (rho=0.110, p=0.04), NE activity (rho=0.168, p=0.01) and MMP-9 (rho=0.175, p=0.01). *Thus, urinary GSA is associated with indicators of neutrophilic inflammation in groups of pwCF. Further investigation is required to determine the kinetics of urinary GSA and how these reflect changes in disease activity in individual pwCF.*

Volume-dependance of Reactance (ΔX) measured with IB-OSC reflects ventilation inhomogeneity.

IB-OSC measures respiratory system mechanics during tidal breathing, with measures of Xrs reflecting volume-dependent changes of individual lung units. Given that Xrs and LCI measures are both governed by the same physiological principles, we determined the ability of X variables to detect VI. 97 children (range 3.3 – 16.7y) attempted paired IB-OSC and MBW measurements. Technically acceptable results on both techniques were achieved by 85 children, with 9 were unable to perform MBW but able to successfully complete IB-OSC, and 3 unsuccessful with both

techniques. A total of 115 paired measurements were included in the final analysis. On average, complete IB-OSC test sessions were achieved in 13 minutes (range 10 – 21 mins) compared to 40 minutes (range 22 – 73 mins) for MBW. LCI ranged from 5.22 to 14.87, with abnormal LCI (≥7.1) identified in 52 measurements (45%). At the time of testing 68/115 (59.1%) pwCF were clinically stable and 47/115 (40.9%) had current respiratory symptoms greater than their usual baseline (our definition of APEx). Overall, children with abnormal LCI results had significantly decreased (more negative) Xrs variables compared to children with normal LCI when results were examined either as a total cohort or when stratified according to clinical status.
Considering LCI as the gold standard measure of VI, we performed ROC curve and used Youden's index to determine optimal cutoff values that gave the best trade-off between specificity and sensitivity for X variables. Figure 2 shows ROC curve analyses (panel A) and comparisons between LCI and ΔX and ΔX/Vt (panel b).

Diagnostic statistics are shown in Table 1. A value of ΔX normalized for tidal volume (ΔX/Vt) ≤ (more negative than) -0.15 gives the best indication that LCI is likely to be abnormal. *In the context of early disease detection, an abnormal ΔX/Vt could be used to indicate which CF children require LCI to enable more effective use of MBW and/or direct treatment once further characteristics including MCID are known.*

Table 1. Results of ROC curve and Youden index analyses to determine ability of IB-OSC to reflect VI

Variable	Cutoff value	AUC	Sensitivity (%)	Specificity (%)	+ LR	- LR
XeE	-1.62	0.76 (0.68,0.83)	75	78	3.38	0.32
ΔX	-0.08	0.77 (0.68,0.86)	73	78	3.29	0.35
ΔX/Vt	-0.15	0.77 (0.68,0.86)	77	78	3.46	0.30

Results expressed as median (25%,75%), AUC: area under ROC curve, LR likelihood ratio. Units: LCI - lung volume turnovers; XeE - $cmH_2O.s.L^{-1}$; ΔX - $cmH_2O.s.L^{-1}$; ΔX/Vt - $cmH_2O.s.L^{-2}$.

Changes in IB-OSC outcome variables track with clinical lung disease.

Both in our previous studies using IB-OSC in wheezy children[20] and in our preliminary data in pwCF, R and X are more abnormal at end-expiration, with values at end-inspiration closer to those seen in healthy controls. In healthy children XeE has a value close to zero (negative or positive). In the setting of peripheral airways disease, the higher elastance at eE (more negative XeE values) indicates mechanical inhomogeneity of peripheral lung units, which improves with inspiration (increasing Xrs), which manifests in negative ΔX and **Δ**X/Vt values. Thus, the magnitude of the difference between XeE and XeI (i.e. ΔX) increases with increasing peripheral lung disease.
We have investigated XeE, ΔX and ΔX/Vt as indices of early lung disease in young children with CF. In grouped data XeE, ΔX, and ΔX/Vt track are significantly worse during APEx. Using data collected from 142 participants, 375 visits, 245 stable, 96 APEx in total, XeE was significantly greater (more negative) [median (25%, 75% -0.97 (-2.37, -0.48) vs -1.76 (-3.89, -0.66), p<0.001] during APEx, as was ΔX [0.12 (-0.23, 0.40) vs 0.09 (-0.60, 0.31), p=0.02], and ΔX/Vt [0.23 (-0.43, 0.64) vs 0.17(-1.67, 0.64), p=0.033]. Considering paired data from consecutive visits for the same child, we have 122 matched pairs while stable and 59 pairs where an APEx visit follows a stable

visit. Median (25%,75%) between test differences for stable visits were 0.04 (-0.41, 0.38) $cmH_2O.s.L^{-1}$ for XeE, -0.06 (-0.46,0.27) $cmH_2O.s.L^{-1}$ for ΔX, and -0.09 (-0.68, 0.43) for $cmH_2O.s.L^{-2}$ for ΔX/Vt. These were significantly lower than those seen for paired stable: Apex visits; 0.18 (-0.14, 0.99, p=0.006) $cmH_2O.s.L^{-1}$ for XeE, 0.16 (-0.24, 0.66, p=0.02) $cmH_2O.s.L^{-1}$ for ΔX, and 0.37 (-0.44, 1.66, p=0.016) for $cmH_2O.s.L^{-2}$ for ΔX/Vt. *In the proposed project we will examine how well these outcome variables perform in detecting early changes in peripheral airway function and early identification of APEx severity.*

Psychosocial measures in ELO

The mental health burden for pwCF and the psychosocial challenges associated with increasing treatment complexity, disease progression, and increased survival, is a research and clinical priority for the wider CF community[49]. Globally, the prevalence of anxiety and depression in pwCF of all ages has been estimated to be approximately 26% (95%CI: 22.1, 30.2) and 14% (11.25, 17.0), respectively[50]. Anxiety and depression are linked to worse health outcomes and reduced survival, and international recommendations around screening and intervention in adolescents and adults have been endorsed and published[51]. Less attention has been given to the psychosocial health in children with CF, and the relationships between age, anxiety/depression, family functioning, resilience, and clinical outcomes are poorly understood[52]. A recent systematic review of anxiety in children with CF identified only 6 studies in children aged 6-12 years and reported the prevalence of anxiety ranged from 28 to 47%[53]: higher than in older patients.
By investigating the relationships between mental health, disease progression, and modifiable psychosocial factors in childhood we may inform early life interventions that seek to improve health outcomes in young pwCF. The instruments that were introduced into ELO 12-18 months ago to address gaps in the literature are: *CF Health Related Quality of Life (CFQ-R)*; *The Child and Youth Resilience Measure (CYRM); The Spence Childhood Anxiety Score (SCAS)*; *The Family Assessment Device (FAD);* and *The Cystic Fibrosis Problem Checklist (CFPC*), with completion rates by eligible participants of 82.3%, 81.7%, 86.7%, 82.3%, and 82.7%, respectively. Based on parental reports, 29.6% of children in the preschool range and 20.2% of school aged children had abnormal SCAS scores. Children scoring above the cut-off thresholds indicating high risk of anxiety/depression are automatically referred for assessment by the clinical team. *These pre-ETI baseline data show that we are documenting a substantial mental health burden and are well placed to show deteriorations or improvements following transitioning to ETI.*

FORMaT Trial Progress

Site set up and opening has been slow due to delays because of the COVID pandemic. Many site ethics and governance offices were prioritising Covid research because of the pandemic, in addition there were research staff deployed to assist with the Covid pandemic response. Platform trials like FORMaT have a resource intensive start-up phase followed by a recruitment phase and delivery of outcomes with ongoing iterative improvements in management as the trial matures. FORMaT has now completed the start-up phase and is well placed to deliver on its outcomes.

Progress in Australia

Ten sites open – The Prince Charles Hospital (CF), Queensland Children's Hospital (CF), Greenslopes Medical Research Foundation (Observation only), Princess Alexandra Hospital, Sunshine Coast University Hospital, Royal Adelaide Hospital, Gold Coast University Hospital (CF paediatrics) and Gold Coast University Hospital (CF adults), Mater Adults Hospital (CF adults) and Royal Perth Hospital (adults). Westmead Children's Hospital is approved and awaiting a site

initiation/activation visit. Governance approvals are pending at Royal Melbourne Hospital, Sir Charles Gairdner Hospital, John Hunter Hospital (Adults and Paediatrics), Perth Children's Hospital. Governance applications are being prepared for the Austin Hospital, St George Hospital and The Alfred Hospital.

Progress for International Sites:

Four sites open –

- Righospitalet, Denmark (CF adults) – Site activated 27th March 2023. Three observation (adult CF) participants recruited to date.
- Singapore has opened 3 sites – however only recruiting to observational cohort at present due to limited funding.

Other international sites ethics/regulatory status

- UK – CF: Local UK Project Manager started in February 2023 and has undergone training with the Brisbane Project Team and local UK team. IRAS application is prepared and is awaiting final checks from the UK team. UK PM has been liaising with sites in the UK regarding trial set up at respective sites. Ten sites have been confirmed they will participate in the UK including: Alder Hey Children's NHS Foundation Trust, Liverpool; Bristol Royal Hospital for Children; Birmingham Children's Hospital; Royal Hospital for Children and Young People, Edinburgh; University Hospital, Southampton; Manchester University NHS Foundation Trust, Wythenshaw; Queen's Medical Centre (Nottingham University Hospitals NHS Trust); Cardiff Adult Hospital. Initial discussions with three Mycobacterial Reference Laboratories (MRLs) in England, Scotland and Wales regarding collection and processing of FORMaT MABS samples.
- France – Contracts are in draft for France. Clinical Trial Application that was submitted in Denmark has been transitioned to the new European Clinical Trial Portal (CTIS) on 21 July 2023. Currently completing a substantial modification and adding France as a new Member State.
- Israel – Six CF sites in Israel are interested in participating in the FORMaT trial pending approval through CFF funding to utilise unspent funds to support the trial in Israel.
- Taiwan – 1 site agreeable to participating in the trial. High rates of MABS-PD in Taiwan. CRA engaged. Currently in process of obtaining funding to support trial set up in Taiwan.

Recruitment:

Recruitment has been slow due to delays with site set up and site opening because of the COVID pandemic. The first Australian site resumed recruitment in first quarter of 2021, and site set up and activation of new sites was able to take place once Covid pandemic restrictions eased. FORMaT has utilized this time to streamline the trial and having now completed the start-up phase and is well placed to deliver on its outcomes.

A total of 46 participants have been recruited over seven sites:

- 30 participants in the Intervention Program (including 3 participants who were transferred from the observation to intervention program) (10 CF paediatrics (all intervention) and 20 adults).
- 19 participants in the Observational Cohort (all adults) – 3 observation participants went to intervention (as above).
- 22 participants have completed the trial.
- 4 participants withdrew from trial prior to completing the Consolidation phase

Sub studies update:

PK sub studies

- All sites are contributing to C1.1 - Steady State Pharmacokinetics of amikacin, where applicable
- 3 sites currently participating for the others (2 adult, 1 paediatric)
- Recruitment: 25 participants consented to all or some of PK sub-studies
    - Of these, 8 have provided samples for micro-sampling and 9 for PK of MABS treatment (all adults – no paediatric samples have successfully been collected to date).
    - Reasons for no sample collection for consented participants: withdrawal of consent during trial, study coordinator unavailable to carry out procedures, incorrect protocol (sample was collected and frozen instead of processed).
- Targeting local sites (South East Queensland) to allow PK sub-study team to provide intensive support.

Immune and Biomarkers sub studies

- 8 sites currently participating in Brisbane and surrounds. RAH participating in Serology and Gene Expression and Denmark participating in Serology.
- 9 serology samples were sent to Denmark in 2022
- 10 samples sent to Melbourne University for Gene Expression processing in April 2023.
- Recruitment: 24 participants have consented to all immune and biomarker sub-studies and one participant has consented to only the gene expression and serology (non-eligible for macrophages function, mitochondrial stress and T-cell function), and 2 have consented only to the Serology substudy.
    - Of these, 41 samples collected for Gene Expression, 53 for Serology, 46 for Mitochondria/Macrophage/T cell.

Imaging sub study

- 7 sites currently participating (6 adult, 1 paediatric)
- Recruitment: 33 participants consented
- Engaged with external imaging providers to assist with FORMaT Trial imaging sub-study
- 50 scans have been sent to Erasmus. Erasmus have checked scan quality and overall are satisfied with image quality. They noted that there were 3 substudy scans that were high in radiation – these were not performed using SSSP. Site feedback was that protocol not clear that Week 12 substudy scans must be performed using SSSP. Version 4 protocol amendment revised to ensure this is clear to sites. Protocol Deviations reported accordingly.

Australian Cystic Fibrosis Data Registry

- 3 sites participating (2 adult, 1 paediatric)
- Recruitment: 8 participants consented
- Plan for Project Team to meet with Database and Registry teams in second half of 2023 to discuss process for data linkage.

Trial committees update:

Drug and Intervention Selection Committee (DISC)

- Membership has been confirmed with 6 external members both nationally and internationally including -USA, Netherlands, Singapore and Sydney. The second meeting took place on the 26st July 2023. FORMaT pharmacist has set up an information and file sharing

platform for all DISC members and is currently assisting DISC Chair in developing an intervention assessment criteria template.

Consumer Advisory Group

- FORMaT CAG was established and first meeting was held on 23rd May 2023 with 4 CAG members present. The aim of the FORMaT CAG is to allow consumer input on the trial – including representation at relevant meetings, reviewing trial documents and grant applications. We currently have 8 CAG members. 5 CAG members have reviewed the trial primary outcome and have agreed this is an important and relevant primary outcome from their perspective. An adhoc meeting in was held on the 18 July 2023 to review the recent NHMRC grant proposal.
- Remuneration for all CAG members has been budgeted and provided to CAG members.

Presentations:

- Scottish Lung in Childhood Meeting – May 2021 – "Pulmonary Mycobacterium abscessus: to treat or not to treat and how should we treat?" – Professor Claire Wainwright
- European NTM conference – July 2021 – "NTM and cystic fibrosis: epidemiology and management of an old enemy" – Professor Claire Wainwright
- Presentation on FORMaT – CFRT – March 2022
- Australia Trials Research Methodology Research Network – Presentation on FORMaT and platform trials – May 2022
- Australian NTM Symposium November 2022 – "Impaired Ability of Macrophages from Cystic Fibrosis in Killing M. abscessus" – Abdullah Tarique
- Presentation on FORMaT – January 2023
- Presentation on FORMaT at Thoracic Society of Australia and New Zealand Conference March 2023. – Dr Megan Rees

SECTION 3: EXPECTATIONS FOR COMING YEAR (not applicable for final report)

What constitutes a significant change in IB-OSC outcome variables?

Before IB-OSC can be used clinically to assess disease in individuals, we need to determine the variability and reproducibility of these variables over time. In the context of CF, we need to understand how IB-OSC outcome variables perform in the absence of changes in disease activity and to determine what change indicates a change in disease status. We will use the data collected at each clinic visit (4 per year) to examine variability, focusing on time points when the participant is clinically stable. Changes in lung function associated with a perceived clinical deterioration from one visit to the next will also be determined. Parents and clinicians will be asked to rate the child's clinical status and older children will also be asked to rate themselves. Data from the subset undergoing IB-OSC home monitoring will be used to establish short- and medium-term day-to-day variability. We will invite 10-15 families living close to QCH to attend for IB-OSC measurements each weekday for 2 weeks (during school holidays) to determine short term reproducibility under laboratory conditions.

Can IB-OSC outcome variables provide early indications of APEx and APEx severity?

A substantial "Holy Grail" in CF management is to be able to predict the onset of APEx and to prevent them from developing to the stage where the patient requires hospitalization, which we know is associated with falls in lung function. Falls in lung function, as measured by spirometry, are often used as a clinical trigger to introduce (or change) antibiotics, intensify airway clearance, and optimize nutrition. With APEx spirometry fails to recover to baseline values in 25% despite conventional treatment, and this has also been described for LCI in both preschool and older children. Irreversible changes have probably occurred in the airways at these times, which may be clinically undetectable at each exacerbation, but the cumulative injury results in progressive loss of lung function. In older

children, increased variability in spirometry from visit to visit indicates that they are at increased risk of losing lung function. This highlights the importance of developing earlier sensitive signals of impending/developing APEx. We will examine differences in IB-OSC X variables between visits (supplemented by home monitoring data) to determine whether differences (absolute values, Z-scores when available) outside the range of normal (represented by 95% LoA) indicate an impending APEx.

Ability of urinary GSA to track and predict APEx onset.
Our preliminary data give confidence that measuring urinary levels of GSA will provide a sensitive biomarker of pulmonary disease activity, in particular neutrophilic inflammation resulting in oxidative lung damage. We will initially use the urine collected at annual review to determine the associations between urinary GSA, lung function, and clinical disease activity. We will then measure GSA in urine samples collected at routine clinic visits to determine the variability between visits as described above.

To describe the psychosocial burden of CF in children aged 6-11y and how these relate to clinical status.

To understand the significance of psychological and behavioural side effects related to the introduction of ETI we will leverage data obtained in the ELO study examining the prevalence of anxiety, depression and psychosocial risk, and protective factors in children with CF. Mental health is a key research priority in CF[49], and we are addressing significant gaps in knowledge that exist around the prevalence of mental health issues in younger pwCF and the relationships with potentially modifiable factors including family functioning, resilience, and health behaviours. Specifically, better understanding of the relationships between psychosocial factors and sensitive markers of disease (described above) in children are anticipated through this study. To date, mental health in young children with CF is poorly researched and a recent systematic review identified only 6 studies reporting on anxiety in <12y age-group. The temporal relationships between development of mental health conditions and disease progression in younger children are largely unknown. To address these questions, we have added several robust, validated instruments to the main ELO study including CFQ-R; CYRM; SCAS; FAD; and CFPC. These instruments are completed by parents and children, where appropriate, and will provide unique cross-sectional and longitudinal data from the QCH clinic prior to transitioning to ETI. A selection of these instruments will also be administered at baseline, 1-, 6-, and 12-months post ETI commencement.

FORMaT Trial – Expectations for 2024

- Publish the Trial Protocol and the Statistical Analysis Plan in early 2024.
- Open the remaining Australian trial sites
- Plan to reach total of 60 intervention recruits by end of 2024
- This will allow interim analysis to occur - potential for suboptimal arm to be dropped and new intervention to be added.
- Open sites and start recruiting in UK, Israel and France.
- Applications for grant funding to local and international institutions for funding international non-CF sites – including MRFF, JPIAMR and NIH, and charitable funding.
- Conference attendance and abstract presentations by project team to facilitate professional development of project team members – abstracts submitted to APRC 2024 in Taiwan and ECFS 2024 in Glasgow.
- Abstract titled “Finding the Optimal regimen for Mycobacterium abscessus treatment (FORMaT trial) - an outline of the first randomised control trial for M.abscessus.” submitted to APRC 2024 was accepted and will presented as an oral abstract presentation by FORMaT investigator Dr A Burke in April 2024.

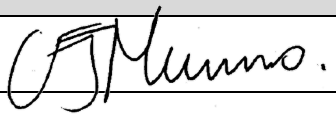
SECTION 4: CERTIFICATIONS

Note: Approvals by email are acceptable but must be provided with the submission as a part of the compiled PDF.

Lead CI or Funding Recipient:

Name	Signature	Date
PETER DAVID SLY		14/02/2024

Head of School/Centre Director:
I have read and endorse this report.

Name	Signature	Date
CRAIG MUNNS		15/02/2024

Submission:

- Email this form, plus your MyBalance Finance Report, as a single PDF to strategicfunding@uq.edu.au.
- Send a separate email for each report submitted.
- Use descriptive subject lines to help categorise emails e.g. {project no} Final/Annual Report.