UQ Strategic Funding Annual/Final Report

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SECTION 1: ADMINISTRATIVE SUMMARY

If this an Annual or a Final Report?	Annual	2022
VC/DVCR Commitment ID (if known):		
Project Title:	Queensland Cystic Fibrosis Research Program (QCFRP)	
Lead CI / Funding Recipient Name:	Professor 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

A. Detailed Progress Report for the year (2022)

1. The scope of work accomplished during the year.

We have had delays in recruiting new participants to the study and have concentrated on collecting as much data at annual reviews and clinic visits as possible. The number of visits completed during 2022 and the number of cumulative visits are shown in the table on page two. The impacts of COVID are clearly seen during 2021 and 2022. Overall, we have completed 200 annual review visits and 362 clinic visits.

Age ranges	Number recruited	Annual Visits				Clinic Visits			
		2020*	2021	2022	Cumulative	2020	2021	2022	Cumulative
<1	5	3	1	0	4	6	5	2	13
1-2	9	5	3	1	9	11	7	4	22
2-3	10	5	5	0	10	2	14	4	20
3-4	13	12	7	3	22	8	15	9	32
4-5	14	12	6	2	20	4	20	8	32
5-6	9	7	2	1	10	1	8	4	13
6-7	15	12	11	6	29	6	17	18	41
7-8	10	7	4	1	12	3	13	5	21
8-9	6	3	2	1	6	2	8	5	15
9-10	9	6	3	3	12	3	11	5	19
10-11	10	6	5	2	13	1	15	7	23
11-12	14	6	4	4	14	4	15	7	26
12-13	8	2	3	1	6	6	8	2	16
13-14	13	6	8	1	15	6	16	11	33
14-15	9	4	4	3	11	5	8	6	19
15-16	3	1	1	0	2	1	4	2	7
16-17	7	3	2	0	5	1	6	2	9
17-18	1	0	0	0	0	1	0	0	1
Total	**165**	**100**	**71**	**29**	**200**	**71**	**190**	**101**	**362**

*not including 38 children who had 'modified annual reviews' during the 2020 lockdowns.

Psychosocial impact of CF lung disease

We have added the following instruments to our data collection to better understand the psychosocial implications of CF and CF lung disease for patients and their families:

- **Health Related Quality of Life (CFQ-R)-** CF specific instrument designed to measure impact on overall health, daily life, perceived well-being, and symptoms. Developed specifically for use in patients with a diagnosis of cystic fibrosis.
- **The Child and Youth Resilience Measure (CYRM)-** A screening tool to explore the resources (individual, relational, communal, and cultural) available to individuals, that may bolster their resilience.
- **The Spence Childhood Anxiety Score (SCAS)-** Assess the severity of anxiety symptoms. The scale assesses six domains of anxiety including generalized anxiety, panic/agoraphobia, social phobia, separation anxiety, obsessive compulsive disorder, and physical injury fears.
- **The Family Assessment Device (FAD)-** Assesses structural and organizational properties of families and the patterns of transactions among family members.
- **The Cystic Fibrosis Problem Checklist (CFPC)-** Developed to assess treatment adherence behaviour in relation to cystic fibrosis.

We started the rollout of these instruments during the year, and they have been enthusiastically received by families, with rates of return averaging around 70% without prompting.

2. The progress of training or work in clinic

The COVID-19 impacts on clinics has diminished but many "visits" are still occurring by telehealth, which limits our ability to collect biological samples and perform lung function testing. We have employed a new research assistant (see Staffing) to improve efficiency in clinic.

Training: Our PhD student is making progress in determining the clinical utility of intra-breath oscillometry, especially in detecting ventilation inhomogeneity (see below).

3. Research progress

a. Urinary biomarkers of neutrophil-induced oxidative stress

Acute pulmonary exacerbations, particularly those requiring hospitalisation, are significantly correlated with loss of lung function and adverse lung health outcomes. There is an increasing need to develop sensitive techniques that accurately reflect current disease activity and predict future risk of exacerbations. This will allow for more appropriate targeting of current and emerging CF treatment strategies thereby improving patient health outcomes and reducing the therapeutic and cost burden for patients with CF.

We have previously shown that exaggerated neutrophilic inflammation and neutrophil-induced oxidative stress are major drivers of early and progressive CF lung disease. We have also previously shown that glutathione sulfonamide (GSA), an irreversible byproduct of glutathione oxidation, provides an index of CF lung disease. Increasing levels of GSA in bronchoalveolar lavage (BAL) and serum samples of patients with CF have been correlated with *P. aeruginosa* infections and radiological bronchiectasis. In addition, we found that 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 results suggest a role for urinary GSA as a non-invasive biomarker capable of identifying and tracking inflammatory disease activity for patients with CF.

To address this question, we followed 102 children (median age 11.5 years, 25%-75% 6.4-14.4) and 64 adults (median age 32.5 years, 25%-75% 25.0-39.0) who were admitted to hospital for management of an acute pulmonary exacerbation and/or eradication of infectious agents such as *P. aeruginosa, S. aureus,* or *Aspergillus*. All participants reported an increase in wet cough and/or sputum production at the time of their admission. Our aim was to explore how urinary GSA levels varied when collected on admission and again on discharge.

GSA was measured by liquid chromatography with mass spectrometry (LC-MS) using multiple reaction monitoring on a Sciex 4000 QTrap. GSA results were reported as medians with 25^{th}-75^{th} percentiles. Differences in urinary GSA results at collection timepoints were compared using Kruskal-Wallis rank test followed by Dunn's method for pairwise multiple comparisons. Paired admission and discharge urinary GSA results were analysed using Wilcoxon signed rank test. Data from children and adults were analysed separately as inflammatory biomarkers vary with disease stage.

Children: 122 admissions were documented during the study period with a total of 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)

Adults: 64 admissions were documented with a total of 124 samples collected: 64 on day 1 of admission and 60 on day of discharge. The mean length of admission was 9 days (SD 3, range 6-19 days)

Table 1: Demographics and clinical characteristics
Results reported as frequency or median (25^{th}-75^{th}%)

	Children (n=171)	Adults (n=64)
Age (y)	12.2 (10.3-13.9)	32.5 (25-39)
Sex (male)	98 (57.3%)	45 (70.3%)
Height (cm)	148.0 (136.0-158.0)	173.0 (166.5-177.5)
Weight (kg)	37.8 (13.0)	64.4 (11.3)
Pancreatic insufficiency	165 (96.5%)	59 (92.2%)
Genotype: copies of p.Phe508del		
2 copies	108 (63.2%)	30 (46.9%)
1 copy	59 (34.5%)	32 (50%)
0 copies	4 (2.3%)	2 (3.1%)
P. aeruginosa		
Not in last 5 yrs	7 (11%)	1 (2%)
Intermittent	42 (68%)	5 (8%)
Chronic	13 (21%)	58 (91%)
S. aureus		
Not in last 5 yrs	11 (18%)	29 (45%)
Intermittent	30 (48%)	24 (38%)
Chronic	21 (34%)	11 (17%)
S. maltophilia		
Not in last 5 yrs	41 (66%)	44 (71%)
Intermittent	17 (27%)	15 (24%)
Chronic	4 (6%)	3 (5%)
M. abscessus		
Not last 5 yrs	56 (90%)	61 (97%)
Intermittent	3 (5%)	1 (2%)
Chronic	3 (5%)	1 (2%)
Aspergillus		
Intermittent	11 (85%)	21 (91%)
Chronic	2 (15%)	9 (9%)
Sputum inflammatory markers		
NE	0.4 (0.4-10.6)	78.3 (23.2-135.7)
IL-8	$4.8x10^3$ ($1.0x10^3$ – $1.6x10^5$)	$2.4\ x10^4$ ($1.2x10^4$ – $4.6x10^4$)
MMP-9	$4.8x10^5$ ($1.3x10^5$ -$1.8x10^6$)	$6.7x10^6$ ($4.5x10^5$ – $1.7x10^7$)
MPO	$7.8x10^6$ ($1.2x10^6$ – $2.9x\ 10^7$)	$3.7x10^7$ ($1.3x10^7$ – $2.2x10^8$)
Serum inflammatory markers		
hsCRP	$2.8x10^5$ ($6.5x10^5$ – $1.3x10^7$)	$1.6x10^7$ ($7.4x10^5$ – $3.6x10^7$)

hsCRP: high sensitivity c-reactive protein; IL-8: interleukin 8; MMP-9: matrix metallopeptidase 9; MPO: myeloperoxidase; NE: neutrophil elastase activity.

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) but not for adults (0.05 [0.03-0.09] µM vs. 0.05 [0.03-0.07] µM, p=0.067). Matched admission-discharge samples were available for 49 children and 60 adults. For 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 results at discharge (compared to

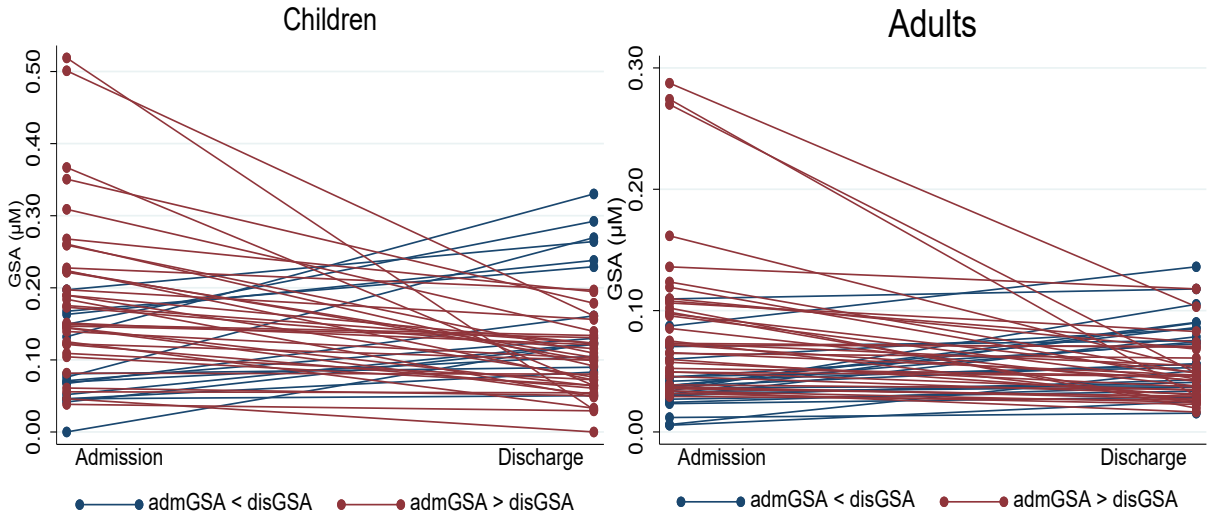
admission), while 15 participants (30.6%) had an increase in GSA results at discharge (Figure 1, left panel). For adults, no statistically significant difference was observed between admission and discharge results (0.05 [0.03-0.09] µM vs. 0.05 [0.03-0.07] µM, p=0.078). Thirty-six participants (60%) had lower GSA results at discharge (compared to admission), while 24 participants (40%) had higher GSA results on discharge (Figure 1, right panel).

We performed Spearman's correlation analysis on GSA results collected at the time of admission with age, height, weight, lung function, infection status (absence vs. presence), and inflammatory markers. Analysis was performed separately for children and adults. No associations were seen between any variables and GSA values for adults. For children, a weak positive correlation was identified between urinary GSA levels 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).

All participants were symptomatic at the time of their admission with an increase in wet cough and/or sputum production. Upon discharge, both children and adult participants showed significant improvements ($p \leq 0.05$) in FEV_1 z-score values, and significantly reduced markers of systemic inflammation (including NE activity, MMP-9 and hsCRP). Reduction of GSA levels following treatment of an exacerbation in children provides strong supporting evidence to urinary GSA as a potential biomarker of pulmonary neutrophil-derived oxidative stress that can be used to non-invasively monitor changes in pulmonary inflammation activity.

Figure 1: Urinary GSA on admission and discharge for acute pulmonary exacerbation

Matched admission and discharge urinary GSA results for children (left panel) and adults (right panel) with cystic fibrosis. Red lines indicate patients who had higher GSA values at admission compared to discharge (69.3% for children and 60% for adults). Blue lines indicate patients who had higher GSA values at discharge compared to admission (30.6% for children and 40% for adults).



b. Assessing ventilation inhomogeneity with intra-breath oscillometry

Respiratory reactance, as measured by oscillometry, reflects energy dissipation during breathing in phase with changes in lung volume. This energy is dissipated against inertive and elastic forces to expand lungs and contains a component of energy dissipation moving gas through the small peripheral airways by diffusion and Brownian motion. As such reactance is influenced by the time constants governing inflation and deflation of individual lung units. These time constants also influence distribution of ventilation in lung units. CF lung disease begins in the lung periphery and ventilation inhomogeneity, as measured by multiple breath washout (MBW) is a sensitive indication of early CF lung disease.

MBW is commonly performed using 100% O_2 to "wash" N_2 from the lung and the primary outcome variable is the lung clearance index (LCI), which reflects the number of lung volume changes required to reduce N_2 to $1/40^{th}$ (or 2.5%) of its starting concentration. LCI has been shown to be more sensitive than spirometry in detecting CF lung disease, especially in young children with mild lung disease. The main problem with MBW is the time taken to achieve adequate data. The ATS-ERS guidelines for measuring LCI in young children recommend having 1-2 hours available to obtain good quality data. This hardly fits into CF clinic routines and has been a barrier to widespread implementation. In addition, success rate varies, being as low as 30% in some reports.

Intra-breath oscillometry (IB-OSC) measures changes in respiratory impedance, partitioned in resistance (R) and reactance (X), occurring during tidal breathing. We use a single 10 Hz sine wave to measure IB-OSC in children, providing as estimate of R and X every $1/10^{th}$ of a second during both inspiration and expiration. IB-OSC can be measured successfully in 80-90% of children as young as 3 years old and reliable data is usually obtained in 10-15 minutes, making this test more feasible for routine use in CF clinics.

The changes in X during lung inflation and deflation, i.e. the volume-dependence of X, provides an indication of ventilation inhomogeneity, as outlined above. We report the values of X at the zero flow points at end expiration (XeE) and end inspiration (XeI). The volume-dependence is reported as the absolute value of the difference between these two (XeE-XeI).

In preliminary studies, we have measured IB-OSC and MBW in 75 children with CF attending the CF clinic at QCH. Acceptable paired IB-OSC and MBW measurements were achieved by 64 children (male 63%), median age 7.1yrs (IQR 4.7-8.6) and height 121.8cms (IQR 108.9-135.1). Abnormal LCI results, $LCI_{2.5\%}$ >7, were reported in n=26 (41%). There were no differences in sex, age, or height between those with normal vs. abnormal LCI results. Children with abnormal LCI results had decreased (more negative) Xrs variables compared to children with normal LCI. A difference was seen for ReE-eI. (Table 2).

Table 2: Resistance and reactance in children with normal or abnormal LCI.

Variables (median, 25^{th},75^{th}%)	**Normal LCI (n=38)**	**Abnormal LCI (n=26)**	**p-value***
ReE	6.72 (5.10, 8.59)	7.93 (5.86, 11.85)	0.11
ReI	5.68 (4.26, 7.03)	6.50 (4.94, 8.54)	0.29
ReE-eI	1.23 (0.78, 1.57)	1.85 (0.79, 2.96)	**0.048**
XeE	-0.95 (-2.47, -0.37)	-2.98 (-4.09, -1.88)	**0.001**
XeI	-1.13 (-1.93, -0.83)	-2.35 (-3.54, -1.59)	**0.005**
XeE-eI	0.18 (-0.08, 0.48)	-0.24 (-1.41, 0.01)	**0.001**
X-slope	-0.36 (-1.24, 0.52)	0.53 (0.02, 3.25)	**0.001**

*p-value calculated using Mann-Whitney U test

R: resistance, X: reactance, eE: end expiration, eI: end inspiration, Xslope: slope of the volume-dependence of reactance (explained below).

These preliminary results suggest that IB-OSC Xrs variables reflect ventilation inhomogeneity. As IB-OSC is more feasible than MBW in very young patients with CF, further research is warranted to explore the potential of IB-OSC in this cohort.

c. Using the volume-dependence of reactance to detect early lung disease

In both our previous studies using IB-OSC in wheezy children and in our preliminary studies in children with CF, we see that larger abnormalities in R and X are seen at end-expiration and that the values at end-inspiration are closer to those seen in healthy controls. We reported that the volume-dependence of R gave the best discrimination between children with airway obstruction and healthy controls. This variable is easy to calculate as R, at end-inspiration and end-expiration, has positive values (R can never have a negative value). However, in healthy children X at end-expiration has a value close to zero and may be

either negative or positive. As the lung inflates, the value of X becomes (more) negative, thus the slope of X plotted as function of tidal volume is negative. With lung disease, the value of X at end-expiration becomes increasingly negative, with a magnitude greater than the value at end-inspiration. Thus, with lung disease the slope of the volume-dependence of X becomes positive. As calculating the slope of the X-volume plot is technically easier than calculating XeE-XeI, we have investigated this as an index of early lung disease in young children with CF.

Using data collected from 142 participants, 375 visits in total, we have examined the difference in the slope of the X-volume plot (X-slope) when patients have been stable vs. experiencing an exacerbation (+/- antibiotic use). Table 3 shows the median and 25th-75th% for X variables. Overall, we have observed more positive X-slopes in patients currently experience an exacerbation (-/+ antibiotic use). Significant differences between all groups, for all X variables were seen. With respect to the X-slope, further analysis revealed significant differences between patients who were stable and those experiencing an exacerbation with antibiotic use (p=0.02).

Table 3: Comparison of reactance measured by IB-OSC in children who were stable or experiencing an exacerbation at the time of testing.

	Stable (n=245)	Exacerbation -Ab (n=34)	Exacerbation +Ab (n=96)	p-value*
XeE	-1.01 (-2.22, -0.42)	-1.78 (-3.37, -0.54)	-1.76 (-3.66, -0.68)	**<0.001**
XeI	-1.19 (-2.11, -0.67)	-1.77 (-2.72, -0.55)	-1.82 (-2.93, -0.97)	**0.001**
ΔX	0.12 (-0.45, 0.33)	-0.004 (-0.57, 0.19)	-0.05 (-0.91, 0.26)	**0.05**
Xslope	-0.23 (-0.66, 0.32)	0.03 (-0.35, 0.69)	-0.09 (-0.57, 1.71)	**0.03**

*p-value calculated using Mann-Whitney U test. X: reactance, eE: end expiration, eI: end inspiration, Xslope: slope of the volume-dependence of reactance.

These preliminary results suggest that the slope of the X-volume plot (X-slope) may be a more sensitive variable for use in detecting early lung disease. Continued research will explore the change in X-slope between visits and ROC curve analysis will be used to identify the most appropriate 'cut point' for this variable.

4. Problems encountered / actions taken

COVID impacts:

a) Recruitment. In 2020 and 2021 The Prince Charles Hospital (TPCH) were severely affected by COVID – the CF ward was taken over as the Covid ward, their research staff were seconded to ward duties, and essentially all outpatient services were suspended. This situation has improved in 2022 but they are not back to full capacity. Similar, but less disruptions were experienced at Queensland Children's Hospital (QCH), with reduced numbers of patients with CF attending clinic and a reduction in the number of admissions for pulmonary exacerbations. In 2021/22, despite Queensland still experiencing new waves/variants of COVID there was an increase in data collection from annual reviews and clinic visits at QCH, and an increased number of MRI scans performed, however the same cannot be said for TPCH. This prompted PI to approach Mater hospital as an alternative adult site, as an increasing number of adolescents with CF transition to adult care at the site. This was approved by CFF 28 June 2022 and Mater Hospital is now formally listed as an adult site. Additionally, TPCH is now able to re-assign staff from COVID duties/clinics to focus on CFF clinics and patients. PI anticipates recruitment and data collection will improve during the next 12 months as clinics return to a more regular schedule with less impact on attendance at both clinics and exacerbation admissions.

b) MRI availability. COVID lockdowns have also limited the times available for research MRI scans. We have optimized the scanning protocol and performed 6 scans in the last month. An initial aim was to have CT and MRI scans performed as close as possible to each other to allow direct comparison. This has proven difficult to achieve, so we have made two changes. 1. Obtaining permission for CT scans to pe performed in the same visit at the research imaging facility that does

the MRI scans. 2. Obtaining permission for access to the clinical MRI scanner at QCH to enable MRI scans to be done on the same day as clinical CT scans. These changes will give access to more MRI scanning spots and enhance our ability to complete this component of the study.

5. Future plans

a. **Point of care biomarkers of disease activity.** Given the promise shown by urinary GSA and the volume-dependence of inertance to indicate early CF lung disease and to track disease activity, we will actively pursue these targets in 2023 in longitudinal analyses to see how well they perform in predicting acute pulmonary exacerbations, potentially allowing early detection, treatment, and prevention.

b. **Lung function in infants with CF.** We have obtained funding for a pilot study (see below) of using IB-OSC for early lung disease detection in the first 2 years of life of children with CF. Our group has a long history of successfully measuring lung function in unsedated infants during natural sleep. We will bring this expertise to bear on this new project. If the data appear promising, they will be used to target further funds to extend the age range of the ELO project down to soon after diagnosis (3-6 months of age).

B. Staffing.

Nelufa Begum, the study statistician left during 2022 to pursue other career options. We have replaced her by sub-contracting statistical services to Co-Investigator Professor Robert Ware's group at Griffith University. Statistical analyses will now be undertaken by Nicholas Rai, under the direct supervision of Professor Ware.

Isabella Andersen (lab RA) has moved on and has been replaced by Sam Frawley.

We recruited a new research assistant, Maddison Deery, with funds from the Child Health Foundation, Queensland, to assist Dr Tamara Blake with study visits. Maddison joined the team in September. We plan for her to take over the Clinical RA duties at the CHRC/QCH site in 2023.

C. Publications/Presentations.

1. Kelk D, Logan J, Andersen I, Gutierrez Cardenas D, Bell SC, Wainwright CE, Sly PD, Fantino E. Neutrophil respiratory burst activity is not exaggerated in cystic fibrosis. J Cyst Fibros. 2022;21:707-712.
2. Begum N, Byrnes CA, Cheney J, Cooper PJ, Fantino E, Gailer N, Grimwood K, Gutierrez Cardenas D, Massie J, Robertson CF, Sly PD, Tiddens HA, Wainwright CE, Ware RS. Factors in childhood associated with lung function decline to adolescence in cystic fibrosis. J Cyst Fibros. 2022. Published online Mar 28. DOI.org/10.1016/j.jcf.2022.008.
3. Blake T, Sly PD, Andersen I, Wainwright CE, Reid D, Bell SC, Kettle AJ, Dickerhof N. Changes in admission-discharge urinary glutathione sulfonamide (GSA) levels in patients with Cystic Fibrosis. Eur Respir J (submitted).
4. Blake T, Wainwright CE, Sly PD. Comparing intra-breath oscillometry and multiple breath washout in children with CF. Presented at Australian Cystic Fibrosis Conference 2022. Awarded best abstract.
5. Blake T, Wainwright CE, Sly PD. Comparing intra-breath oscillometry and MBW in children with CF. Presented at TSANZRS Annual Scientific Meeting 2022. Awarded best oral presentation on Cystic Fibrosis.

Additional outcomes

New Funding awarded

a. Blake T. Improving detection and assessment of lung disease in young children with Cystic Fibrosis. Australian Cystic Fibrosis Research Trust. $80,000, 2022.
b. Blake T. Predicting and preventing acute pulmonary exacerbation in young children with cystic fibrosis. Early Career Academic Fellowship. Child Health Foundation. $200,539, 2022-24

D. Invention Disclosures/Patents.

Nil

E. For research projects supported by multiple awards, please indicate the **estimated percentage of CFF support** to the total.

Not applicable

FORM*a*T trial (Prof Claire Wainwright)

Trial progress to date:

Despite the delays to the set up of the FORMaT trial internationally, there have been significant trial achievements including the following:

- Employment of the FORMaT trial management team, statistical analysis team and trial database management team.
- Statistical simulation modelling for the trial was performed.
- Trial protocol and essential trial documentation developed.
- Complex trial database in REDCap was designed, including extensive testing of the randomisation programs prior to the database going live.
- Safety database designed with extensive testing to ensure accurate and timely safety notification and reporting to investigators and relevant authorities.
- Established the trial oversight committees (including iDSMB, TSC, Trial Management Committee and the Drug and Intervention Selection Committee)
- Trial registration established and updated protocol publicly available (NCT04310930).
- Trial opened and recruiting in 5 trial sites in Australia, which included ethics and governance submissions and approvals as well as regulatory approval through the Therapeutic Goods Administration (TGA). ○ Further 2 Australian sites approved through ethics, granted site specific governance approval and will be activated for recruitment shortly.
- Further 6 Australian sites approved through ethics and awaiting governance approval.
- To date, 27 subjects have been recruited: 19 to the intervention cohort (age range from infancy through to >80 years), with 4 subjects having completed the trial - intervention (2) and observational (2) cohorts.

A major protocol amendment will be finalised shortly. The amendment includes modularisation of the trial protocol to allow flexibility in trial sites to partake in the modules that are feasible at their site. This will allow research objectives to be addressed quicker with higher recruitment rates to specific modules.

Internationally, the trial has been granted conditional approval in Denmark by the Danish Medicines Agency and Danish Ethics Committee. Contracts are in place for the UK sites and a a UK project manager has been appointed. Preliminary meetings with the French investigator team occurred in June 2022. Translation services have been engaged to assist with translation of participant facing

documents for relevant international sites. Monitoring processes for international sites have been developed through local authorities using central and risk-based approaches, and by establishing the on-line secure SiteDocs platform to enable remote monitoring as required.
Three potential industry partners have approached the FORMaT trial to discuss new intervention arms, specifically two new intravenous therapies (ceftazidime-avibactam and imipenem-relebactam) and one new oral therapy (omadacycline).

Plan for trial progress for next 3 years
Recruitment of subjects has been well below anticipated due to the SARS-CoV-2 pandemic. However, recruitment has now improved to the anticipated level because trial sites have been opened in Australia and pandemic restrictions have eased. We estimate a recruitment rate in Australia of 50 participants per year in 2023/24.
It is anticipated that the Copenhagen site in Denmark will be opened and recruiting before the end of 2022. Contracts will aim to be established with the French network before the end of 2022, and it is anticipated that the regulatory and ethical submissions in France will follow the approval of the updated modularised protocol version 4. The French submissions will be facilitated using established documentation from the Danish Medicines Agency and Danish ethics committee applications. The first priority for the newly appointed UK project manager will be completing the regulatory and ethical submissions to obtain approval to open the trial at the proposed UK trial sites.
Once sites in the UK, Denmark and France are established (anticipated by July 2024), contracts and regulatory applications will be undertaken for other CFF funded countries including Ireland (led by Professor Edward McKone, St. Vincent's Hospital Dublin), and Canada (Drs Elizabeth Tullis, St. Michaels Hospital Toronto; Ted Marras, Toronto Western Hospital; Professor Felix Ratjen, Sick Kids Hospital Toronto).
Approval of the next major protocol amendment will allow the trial to be expanded to trials sites in Singapore and Japan as they are able to partake in the protocol modules that are feasible locally and predominantly for non-CF participants. Funding for non-CF participants will come from other grant processes not from CFF but it will enable more rapid trial participation and more rapid answers to the research questions overall.
Internationally, we anticipate recruitment of up to 10 subjects in 2022-2023 increasing to 20/year in 2023-24 and up to 50/year by 2027-2028. Based on these rates, by the end of 2024, we would have achieved the planned 100 subjects to have completed the Intensive treatment phase of the trial. This would enable the first interim analysis to be undertaken. In addition, a new arm for intensive therapy could be added to the trial. By the end of 2025, 100 subjects should have also completed the consolidation therapy, at which point we anticipate a new arm established for the consolidation treatment phase.
The core funding for the trial includes ongoing salary support for the FORMaT project management, statistical analysis and database management teams as the funding has been expended to date as per the original CFF budget. Core funding was also obtained through the Australian government funding scheme MRFF administered through NHMRC. The contribution from both grants enabled both CF and non-CF participants to be recruited in the trials and both grants have contributed to the core funding. The MRFF grant will come to an end in June 2023 and an application for ongoing funding has also been submitted to NHMRC with results expected in the first quarter of 2024. We have taken great care not to "double dip" and the budgets can be clearly separated although both are essential to ensure that the trial can continue. If the NHMRC application is successful it will only provide support for Australian participants and some core funding as did the previous application and we are happy to send CFF the NHMRC application and budget for clarity if successful.
The FORMaT teams are essential to ensure the ongoing trial set up and activation of trial sites in Australia and internationally, management of the main trial and safety databases, completion of the

statistical analysis plan and carrying out the interim and ongoing analyses of the trial data. Supporting the ongoing progress of the FORMaT trial will also ensure that novel treatments may be added to the trial.

The COVID-19 pandemic has highlighted the importance of platform trials and demonstrated the importance of pragmatic approaches, such as modularising trials to facilitate trial roll out and data collection. It is now well recognised that adaptive platform trials are extremely resource intensive particularly at the start-up phase and this complex trial is now running successfully despite the slow start.

Proposed Trial Time line

Oct 2022- Sept 2023	Additional Sites Open	14 Australian sites
	Additional Sites Open internationally	Open sites in 4 countries (Denmark- 1 site, UK- 7 sites)
	Recruitment	50 Australian participants/ year 10 international participants/ year
	Drug intervention and selection committee	Selection of new intervention arm for SI prepared
	Industry	Initial Contracts
October 2023 to September 2024	Additional Sites Open internationally	Open sites in 4 countries (France- 4 sites, Singapore- 1 site)
	Recruitment	50 Australian participants/ year 20 international participants/ year
	Grant applications for non-CF international funding	Plans for sites in Taiwan, Japan, South Korea
October 2024 to September 2025	Interim Analysis	For Short Intensive therapy Minimum of 100 subjects completed short intensive (SI) and 30 subjects in observation completed study
	Simulations	Update simulations for SI (BAR, potential to drop an ineffective arm, addition of a new intervention)
	Drug intervention and selection committee + trial management committee	Detailed proposals for SI new intervention
	Trial Steering Committee (TSC) + Data Safety Monitoring Board (DSMB)	SI- consideration of dropping an ineffective arm (if required), addition of a new intervention
	Updated SI protocol and PICF	Submissions to HREC, governance, regulatory bodies
	Recruitment	50 Australian participants/ year 30 international participants/ year Minimum of 100 subjects completed Consolidation.
	Drug intervention and selection committee	Selection of new intervention arm for Consolidation
	Regulatory completion and contracts	Canada and Ireland
	Trial registration	Updated for SI

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

The funding allocation for 2022 will follow the initial proposal. This covers mainly gaps in staff funding and allows additional positions not covered by CFF or CHF funds

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 D Sly		18/01/2023

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

Name	Signature	Date
Craig Munns		

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.