Cardiology in the Young

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Original Article

Cite this article: McCay N, Beirne N, Bereton E, Healy M, and Franklin O (2024). COVID-19 and PIMS-TS-related admissions to paediatric intensive care in the Republic of Ireland January 2020 and July 2022 and analysis of cardiovascular manifestations of their disease. *Cardiology in the Young*, page 1 of 6.
doi: 10.1017/S1047951124025733

Received: 25 March 2024
Revised: 28 June 2024
Accepted: 25 July 2024

Keywords:
PIMS-TS; COVID-19; cardiac; paediatric intensive care

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COVID-19 and PIMS-TS-related admissions to paediatric intensive care in the Republic of Ireland January 2020 and July 2022 and analysis of cardiovascular manifestations of their disease

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Abstract

Background and aims: Our aim was to investigate all children admitted to paediatric intensive care units (ICU) in the Republic of Ireland between January 2020 and August 2022 with an admitting diagnosis of acute COVID-19 infection or paediatric inflammatory multi-system syndrome, temporally associated with SARS-CoV-2 (PIMS-TS) or associated illness. The patients were identified to catalogue the severity of illness, analyse cardiovascular manifestations of their disease, and short-term outcomes. *Methods:* This is a retrospective multi-centre observational study. *Results:* 127 children were admitted to paediatric ICU in Ireland with a COVID-19- related illness between January 2020 and August 2022. 87 (68.5%) of patients had acute COVID-19 infection, 39 (30.7%) had PIMS-TS and 1 (0.8%) patient had post-COVID vaccine-related myocarditis. Ventilatory support was required for 47/87 (54%) in the COVID-19 group comparative to 9/39 (23%) of patients with PIMS-TS. Inotropic support was required for 13/87 (14.9%) children with COVID-19 and 29/39 (74.3%) with PIMS-TS. Evidence of any cardiac disease on ECHO was identified in 23/38 (60.5%) of the PIMS-TS cohort comparative to only 5/36 (13.9%) of patients with COVID-19. 38/39 (97.4%) of patients with PIMS-TS-related cardiac disease and 100% with COVID-19 had a normal echo at the time of discharge from hospital. Overall survival of patients was 100%. *Conclusion:* The burden of cardiac disease in children requiring paediatric ICU care for COVID-19-related disease was high in the acute phase; however, all children survived, and all cardiac investigations had normalised by short-term follow-up.

Introduction

It became clear as the COVID-19 pandemic unfolded children suffered cardiovascular complications of both acute and sub-acute COVID-19 infection.

Our aim was to investigate all children admitted to paediatric ICU in the Republic of Ireland between January 2020 and August 2022 with an admitting diagnosis of COVID-19 or Paediatric Multisystem Inflammatory Syndrome—Temporally Associated with SARS-CoV-2 (PIMS-TS) or associated illness. The patients were identified to catalogue the nature and severity of illness and analyse cardiovascular manifestations of their disease.

Materials and methods

Patients admitted to paediatric ICUs at Children's Health Ireland (Crumlin and Temple Street) January 2020 and August 2022 with acute COVID-19 infection and PIMS-TS were identified from the Irish Paediatric Intensive Care Audit Network and Intellispace Critical Care Dataset. The electronic patient record was used to collect demographic data diagnosis; co-morbid conditions; treatment; and outcome. We described and compared the cardiac manifestations of these diseases including echocardiogram findings at time of acute illness and at the time of hospital discharge. Additionally, we analysed cardiac biomarkers and electrocardiographs in the patients with PIMS-TS.

Diagnostic uncertainty remains in the area of paediatric COVID-19 and associated illness, particularly where there is no laboratory evidence of acute SARS-CoV-2 at the time of admission. For clarity, admitting diagnostic definitions and inclusion criteria are as follows:

Acute COVID-19 infection definition[1]

A diagnosis of acute COVID-19 was made where there was a positive SARS-CoV-2 reverse-transcriptase protein chain reaction at the time of admission. This included patients with a positive laboratory finding in the setting of a non-respiratory illness, for example, status epilepticus and diabetic ketoacidosis.

PIMS-TS RCPCH definition[2]

A diagnosis of PIMS-TS was made where a child met the following clinical criteria: persistent fever, inflammation (neutrophilia, elevated CRP, and lymphopaenia) with evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal, or neurological disorder) with additional features.

- This may include children fulfilling full or partial criteria for Kawasaki disease.
- Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal, or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus.
- SARS-CoV-2 PCR testing may be positive or negative.
- A history and/or serologic evidence of SARS-CoV-2 prior infection or recent exposure is helpful in establishing a working diagnosis of PIMS-TS in context of the clinical picture described.

During retrospective analysis of each case, where uncertainty remained as to how each patient should be categorised according to their working diagnosis, two clinicians and one data manager reviewed each case independently before assigning the appropriate categorisation.

Echocardiograms were reviewed by cardiologists and cardiac function was classified according to the American Society of Echocardiography and the European association of cardiovascular imaging (Table 1).[3]

Due to the small numbers of cases, descriptive data are presented as numbers and percentages in tabulated form, with simple statistical analysis. All data were irreversibly anonymised and handled in accordance with data protection regulations. This study is registered with and approved by the Paediatric Intensive Care Department Research Committee, Children's Health Ireland at Crumlin.

Results

There was a total of 127 admissions to paediatric ICU in Ireland over a 32-month period with a working diagnosis of acute COVID-19, PIMS-TS, or related illness. Figure 1 illustrates the varying rates of admission to PICU in the Republic of Ireland with COVID-19 related illnesses between January 2020 and August 2022.

87 (68.5%) patients admitted had a working diagnosis of COVID-19. 39 (30.7%) of patients had a working diagnosis of PIMS-TS. One patient (0.8%) was admitted with a working diagnosis of myocarditis, however, as it was temporally related to COVID-19 vaccine administration this patient was included.

Age, and ethnicity

Of the 87 patients with acute COVID-19 illness 51/87 (59%) were <5 years of age, 17/87 (20%) were aged 6–10 years, and 19/87 (21%) were aged 10–15 years. From an ethnicity perspective, 76/87 (87%) were documented as White and 10/87 (11%) were documented as Black, Asian, and Ethnic Minority. One patient had no ethnicity documented.

Of the 39 patients admitted with PIMS-TS, 8/39 (21%) were <5 years of age, 15/39 (38%) were aged 6-10 years and 16/39 (41%) were aged 10–15-years. Reviewing ethnicity in this group 25/39 (64%) were documented as White and 14/39 (36%) were documented as Black, Asian, and Ethnic Minority.

Co-morbidities

In the COVID-19 group, 52/87 children (60%) had documented co-morbidities, the majority of which 33/87 (38%) were non-respiratory in nature. 15/87 (17%) had respiratory co-morbidities, e.g., cystic fibrosis or asthma. Immunosuppression (i.e., chemotherapy in oncology or anti-rejection medication in transplant) was ongoing for 2/87 (2%) of children (2%). A high BMI was documented in 2/87 (2%) children.

In the PIMS TS group. 8/39 (21%) had co-morbidities, the majority 3/39 (8%) of which were non-respiratory in nature. No patients were known to be immunosuppressed, 1/39 (3%) children had a respiratory co-morbidity and 4/39 children (10.2%) had a documented high BMI.

Ventilatory support and interventions

Ventilatory support was required for 47/87 (54%) patients in the COVID-19 cohort. Mechanical ventilation was required for 36/87 (41%) patients and non-invasive ventilation for 11/87 (13%). Inotropic support was required for 13/87 children (14.9%). Steroids and Intravenous Immunoglobulin (IVIG) were used in 37/87 (42%) and 11/87 (13%), respectively, in line with best evidence available at the time.

In the PIMS-TS group, ventilatory support was required for 9/39 (23%) of patients. Mechanical ventilation was used in the case of 8 (21%) patients and non-invasive ventilation in just 1 (3%). Inotropic support was required in 29/39 (74.3%) of patients, 37/39 (95%) of these children received steroids and 31/39 (77%) IVIG.

Outcomes

No child died as a direct result of acute COVID-19 infection while in paediatric ICU. One patient with a positive SARS-COV-2 PCR did not survive to discharge from paediatric ICU; however, COVID-19 was not deemed to be a primary cause of death.

There was 0% mortality in paediatric ICU for children with PIMS-TS. No child died prior to hospital discharge.

Cardiac manifestations results

Impaired left ventricular systolic function

36/87 (41.8%) patients with COVID-19 infection had an echocardiogram (ECHO) during their admission to paediatric ICU. 5/36 (13.9%) had evidence of impaired left ventricular systolic function on initial echo, 4/36 (11.1%) had mild left ventricular systolic dysfunction and 1/36 (2.8%) had severe dysfunction. 31/36 (86.1%) of the COVID-19 infected children, who had an ECHO performed, had documented normal left ventricular systolic function.

38/39 (98%) PIMS-TS patients had an echocardiogram during admission to paediatric ICU. 14/38 (36.8%) had evidence of reduced left ventricular systolic function, 8/38 (21%) of patients

https://doi.org/10.1017/S1047951124025733 Published online by Cambridge University Press

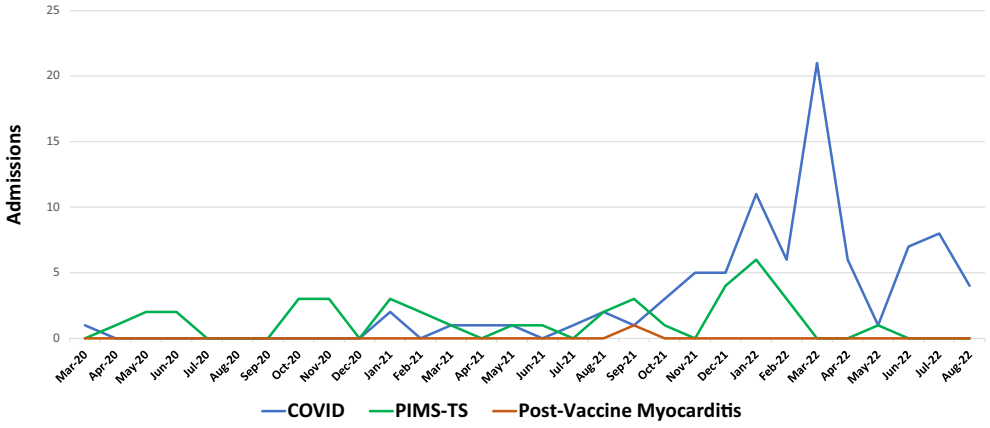

Figure 1. COVID-19 + / PIMS-TS PICU Admissions Republic of Ireland January 2020 to August 2022.

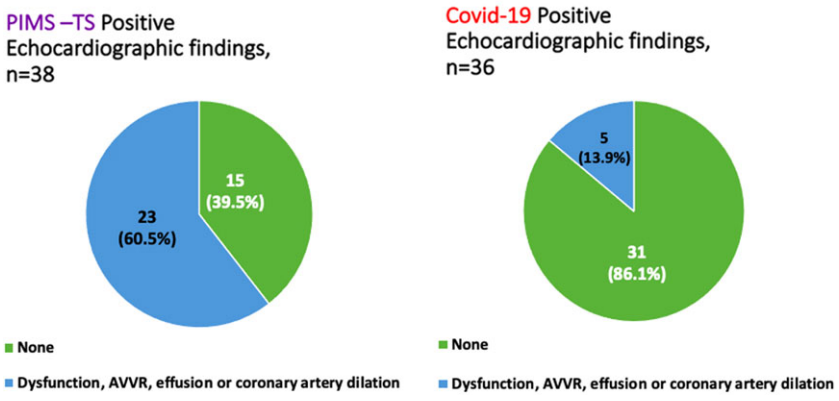

Figure 2. Evidence of cardiac disease on trans thoracic echocardiogram in the PIMS-TS patents comparative to the patients with COVID-19 infection.

had mildly reduced left ventricular systolic function and 6/38 (15.8%) moderately reduced left ventricular systolic function. There were no patients with PIMS-TS that had severely reduced left ventricular systolic function. 24/38 (63.2%) of the PIMS-TS cohort had normal left ventricular systolic function.

Pericardial effusion, coronary artery dilation, or atrioventricular valvar regurgitation

No COVID-19 patients had evidence of pericardial effusion, coronary artery dilation, or atrioventricular valvar regurgitation.

8/38 (21.1%) of patients with PIMS-TS had pericardial effusion. Where pericardial effusion was identified, there was other evidence of cardiac inflammation in most cases, 7/38 (18.4%) of patients with PIM-TS had pericardial effusion in addition atrioventricular valvar regurgitation, reduced left ventricular systolic function or coronary artery dilation. Pericardial effusion was an isolated finding in only one case (2.6%).

5/38 (13.2%) of PIMS-TS patients had evidence of coronary artery dilation on initial echocardiogram, defined as dilation equating to a z-score greater than + 2. Of note coronary artery changes were more likely to be found in a younger patient cohort. The mean age of patient with coronary artery changes and PIMS-TS was 4.56 years (1.7–7.8 years) comparative to the overall mean age of the PIMS-TS group of 9.3 years (2–15.4 years).

12/38 (31.6%) of PIMS-TS patients had atrioventricular valvar regurgitation on initial ECHO. This was defined as atrioventricular valvar regurgitation that was mild + or more significant. In 7/38 (18.4%) of patients this is an isolated finding and 5/38 (13.2%) of patients had mild + atrioventricular valvar regurgitation with evidence of reduced left ventricular systolic function.

Cardiac disease on transthoracic echocardiogram

Evidence of any cardiac disease on ECHO, including left ventricular systolic dysfunction, atrioventricular valvar regurgitation, coronary artery dilation and pericardial effusion was identified in 23/38 (60.5%) of the PIMS-TS cohort comparative to only 5/36 (13.9%) of patients with COVID-19 (Figure 2).

Echocardiogram at follow-up

38/39 (97.4%) of patients with PIMS-TS-related cardiac disease and 100% with COVID-19 had a normal echo at the time of discharge from hospital.

The persistent echocardiogram changes represent one patient with PIMS-TS with residual left coronary artery dilation.

Cardiac medication on discharge

Only 1/38 (2.6%) PIMS-TS patient with reduced cardiac function on initial ECHO was discharged with an ACE inhibitor. This was subsequently discontinued at outpatient review.

Analysis of electrocardiograph findings on patients with PIMS-TS

21/39 PIMS-TS patients had electrocardiograms that were taken in the acute phase of their illness that were available for retrospective review. 13/21 (61.9%) of these were normal. 8/21 (38.1%) were

https://doi.org/10.1017/S1047951124025733 Published online by Cambridge University Press

Table 1. PIMS-TS biochemistry results

	PIMS TS patients (%) $n = 16$	
Normal nt pro BNP (<300 pg/ml)	4 (25%)	
Raised nt pro BNP	12 (75%)	
	Nt pro BNP 300–500	0
	Nt pro BNP > 500	0
	Nt pro BNP > 1000	3 (25%)
	Nt pro BNP > 5000	9 (75%)
	PIMS TS patients (%) $n = 25$	
Normal CK (30–220 U/L)	18 (72%)	
Raised CK	7 (28%)	
	CK 220–500	2 (28.6%)
	CK > 500	5 (71.4%)
C-reactive protein (mg/L)	PIMS TS patients (%), $n = 39$	
Normal CRP (<5)	1 (2.6%)	
Raised CRP	38 (97.4%)	
	CRP < 100	8 (21.0%)
	CRP > 100	13 (33.3%)
	CRP > 200	13 (33.3%)
	CRP > 300	4 (10.3%)

Table 2. PIMS TS troponin results

	PIMS-TS patients Crumlin (%) $n = 26$		PIMS-TS patients Temple Street (%) $n = 9$	PIMS-TS total (n = 35)
Normal troponin (<14)	6 (23.1%)		1 (11%)	7 (20%)
	Normal troponin and abnormal ECHO	2 (33.3%)*		
Raised troponin	20 (76.9%)		8 (89%)	28 (80%)
	Troponin < 100	12 (60%)	4 (50%)	
	Troponin > 100	3 (15%)	2 (25%)	
	Troponin > 200	1 (5%)	0	
	Troponin > 300	4 (20%)	2 (25%)	

abnormal, 7/21 (33.3%) illustrated an abnormal ST segment or T wave pattern, 1/21 (4.7%) illustrated first degree heart block.

All patients with abnormal inpatient electrocardiograms had normal electrocardiograms by the time of discharge and at follow-up at outpatient clinic.

PIMS-TS patients and biochemistry results

All PIMS-TS patients had a c-reactive protein measurement at the time of their admission, it was raised (>5) in 38/39 (97.4%) of cases. 8/39 (20.5%) of patients had a raised c-reactive protein < 5–100, 13/39 (33.3%) of patients had a c-reactive protein between 100-200, 13/39 (33.3%) between 200-300 and 4/39 (10.3%) of PIMS-TS patients had a c-reactive protein greater than 300 (Table 1).

25 patients (64%) with PIMS-TS had a creatinine kinase measured during their inpatient course. Of those 18/25 (72%) of PIMS-TS patients had a normal creatinine kinase level between 30 and 220. 7/25 (28%) of patients that had a creatinine kinase level that was elevated level, 2/25 (8%) had a level between 220 and 500 and 5/25 (20%) had an elevated level greater than 500 (Table 1).

16/39 (41%) of patients with PIMS-TS had a nt-pro BNP analysed during their admission. 12/16 (75%) of PIMS-TS patients had a raised nt-pro BNP. The raised nt-pro BNP level was between 1000-5000 in 3/16 (18.8%) of patients and >5000 in 9/16 (56.3%) of patients with PIMS-TS (Table 1).

Troponin levels were measured in 35/39 (68.4%) of cases of PIMS-TS (Table 2). Troponin testing differed between the two Paediatric ICUs involved in this multi-centre cohort study. The first centre tested troponin I and the second centre, which included the cardiac paediatric ICU, tested troponin T. Overall troponin was raised in 28/35 (80%) of PIMS-TS patients. There were two patients with normal troponin levels with an abnormal ECHO; the first had only mild cardiac dysfunction with a fractional shortening of 26% but notably a CRP of 226, the second patient had significant AVVR and coronary artery dilation on ECHO and CRP of 293.

Discussion

COVID-19-related illness between January 2020 and July 2022 accounting for 4.3% of national PICU admissions. The Omicron variant spike late 2021-mid 2022 resulted in a significant increase in admissions to paediatric ICUs in Ireland with both primary COVID-19 disease and with PIMS-TS. However, a reduction in PIM-TS cases was noted from early 2022. Reasons for this dissociation between primary COVID-19 illness and PIMS-TS admissions include evidence that there have been critical mutations in the virus superantigen motifs speculated to trigger the hyperinflammatory response.[4] The result being that the evolving mutations in the COVID-19 virus are less likely to trigger a hyperinflammatory reaction.[4] The reducing rates of PIM-TS are also felt to be attributable to increased immunity levels in the community through increased COVID-19 exposure and the uptake of vaccination in children. Vaccination of the paediatric population in the Republic of Ireland began in September 2021 with those aged 12–15 years and was followed in January 2022 for children 5–11 years.[5] It is felt that this increased immune exposure has reduced the development of the aberrant immune response to COVID-19, which is speculated as a cause of PIMS-TS.[2] By 24 July 2022, 24% of 5–11-year-olds and 74.4% of 12–15-year-olds in the Republic of Ireland were fully vaccinated.[5]

The majority of PIMS-TS patients admitted to Irish paediatric intensive care units were previously fit and well with no past medical history of note.

There was a potential significance for susceptibility to this post-covid inflammatory condition see within the Black, Asian, Ethnic Minority groups which represented 36% of the PIMS-TS group requiring intensive care support although only represent 17.9% of the Irish population overall.[6] Unfortunately, our study was not sufficiently powered to assess the significance, but our observation is in keeping with studies word-wide.[7,8]

The retrospective nature of this study limits the analysis of the cardiac manifestations in PIMS-TS. This rare but serious illness was first identified in April 2020 and the world's medical

https://doi.org/10.1017/S1047951124025733 Published online by Cambridge University Press

community had to collaborate, sharing learning and experience with this disease to best determine appropriate investigations and treatment strategies to manage these patients. As our knowledge regarding PIMS-TS evolved so did our testing and treatment strategy. Our biochemistry testing of troponin T and nt-pro BNP developed over the pandemic, and we became more rigorous in our assessment of patients with cardiovascular manifestations of the disease with use of both electrocardiography and echocardiogram testing. The evolving nature of our knowledge of PIM-TS may explain why not all patients had the same investigations. Interestingly, all our PIMS-TS paediatric ICU cohort had a C-reactive protein tested and all had an echocardiogram. The most sensitive biomarkers in our PIMS-TS cohort were C-reactive protein and troponin.

The study illustrated notable differences between primary COVID-19 infection and PIMS-TS. The results indicate that acute COVID-19 infection primarily affected the respiratory system with patients much more likely to require ventilatory support comparative to those with PIMS-TS. Whereas patients with PIMS-TS were more likely to require cardiovascular inotropic support management in paediatric ICU. This level of intensive care support required within the PIMS-TS cohort compares to that seen in previous studies.[9,10]

The dominance of cardiovascular manifestation in PIMS-TS was demonstrated through cardiac disease on echocardiogram. Our comparative study exhibited similar results to the large US Cohort study published in JAMA in 2021 by Feldstein et al,[10] which showed the dominance of the cardiovascular manifestations in PIMS-TS comparative to COVID-19. This large study involving 1116 patients also showed comparable levels of reduced left ventricular systolic function in the PIMS-TS cohort at 34.2% compared to 36.8% in our study and coronary artery dilation in 13.4% compared to 13.2% in our smaller study.[10]

The patients with Kawasaki-type PIMS-TS illustrated by evidence of coronary artery dilation on echocardiogram were a younger group compared to the PIMS-TS cohort overall. Review of the clinical history of this small patient group revealed 3/4 (75%) patients whose clinical notes were available for retrospective review would also have met American Health Association (AHA) guidelines for diagnosis of Kawasaki disease.[11] This highlights the difficulty with the identification of this disease during the pandemic when clinical criteria compared so closely to that for Kawasaki disease, and there is undoubted overlap between them. It could be suggested the only defining feature of post covid Kawasaki PIMS-TS versus Kawasaki disease was the presence of COVID-19 antibodies or evidence of recent exposure to COVID-19 infection but as previously stated that is not an essential part of the diagnostic criteria. As the treatment strategies for Kawasaki disease and PIMS-TS are identical, and all patients are followed by a cardiologist, the clinical relevance of this distinction is minimal.

World-wide reporting of normalisation of left ventricular systolic dysfunction[9,10,12–18] was a reassuring factor when managing the previously well PIMS-TS paediatric population with severe acute cardiovascular manifestations of this disease. Our study also reported all patients with evidence of reduced left ventricular systolic function on initial echocardiogram had returned to normal at short-term follow-up. We had one patient with persistent left coronary artery dilation which is in keeping with the large US cohort study where 20.9% of patients with coronary artery dilation had persistent changes >30 days from diagnosis.[10]

It is hypothesised that given the recovery of left ventricular function within a few weeks of diagnosis that the mechanism of action of myocardial dysfunction in PIMS-TS is likely to be secondary to severe inflammation rather than secondary to ischaemia or myocardial injury. However, data have been produced that suggests that following both primary COVID-19 disease and following PIMS-TS there may be subclinical myocardial injury that may be present even in the setting of a normal left ventricular ejection fraction on echocardiogram.[19,20] To better understand the long-term implications on the myocardium, a large multi-centre cohort study is required to evaluate the myocardial diastolic function and myocardial fibrosis through detailed medium- to long-term imaging and assessment.[10]

Our outcome of 0% mortality at the time of discharge from paediatric ICU is better than that reported worldwide in both the PIMS-TS and COVID-19 paediatric population. Larger studies have reported mortality rates around 1–2%.[10]

Conclusion

The burden of cardiac disease in children requiring paediatric ICU care for acute COVID infection and PIMS-TS was high in the acute phase. However, it remained a relatively mild disease overall in the childhood population with respect to paediatric critical care with reported 100% survival in our cohort of patients in paediatric ICU in the Republic of Ireland. Reassuringly, all cardiac investigations had normalised at the time of short-term follow-up. Medium- and long-term follow-up is required to determine if there are any lasting effects on the paediatric population.

Acknowledgements. None.

Financial support. None.

Competing interests. None.

Ethical standards. The authors assert that all procedures contributing to this work complied with ethical standards and was reviewed and passed by the ethics and research committee at Children's Health Ireland, Dublin, Ireland.

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