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Abstract

The European Cystic Fibrosis Society Clinical Trial Network (ECFS-CTN) has established a Standardization Committee to undertake a rigorous evaluation of promising outcome measures with regard to use in multicentre clinical trials in cystic fibrosis (CF). The aim of this article is to present a review of literature on clinimetric properties of the infant raised-volume rapid thoracic compression (RVRTC) technique in the context of CF, to summarise the consensus amongst the group on feasibility and answer key questions regarding the promotion of this technique to surrogate endpoint status.

Methods: A literature search (from 1985 onwards) identified 20 papers that met inclusion criteria of RVRTC use in infants with CF. Data were extracted and tabulated regarding repeatability, validity, correlation with other outcome measures, responsiveness and reference values. A working group discussed the tables and answered 4 key questions.

Results: Overall, RVRTC in particular forced expiratory volume in 0.5 s, showed good clinimetric properties despite presence of individual variability. Few studies showed a relationship between RVRTC and inflammation and infection, and to date, data remains limited regarding the responsiveness of RVRTC after an intervention. Concerns were raised regarding feasibility in multi-centre studies and availability of reference values.

☆ Take home message: Since early respiratory interventions are needed to improve outcome in infants with cystic fibrosis, standardization and implementation of the RVRTC technique are needed before RVRTC can be used as primary outcome in clinical trials.

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Conclusion: The ECFS-CTN Working Group considers that RVRTC cannot be used as a primary outcome in clinical trials in infants with CF before universal standardization of this measurement is achieved and implementation of inter-institutional networking is in place. We advise its use currently in phase I/II trials and as a secondary endpoint in phase III studies. We emphasise the need for (1) more short-term variability and longitudinal 'natural history' studies, and (2) robust reference values for commercially available devices.

Keywords: Infant pulmonary function; Cystic fibrosis; Clinical trials; Surrogate outcome; Clinimetric properties; Raised volume rapid thoracic compression

Contents

1. Introduction

With the increasing availability of newborn screening (NBS) for cystic fibrosis (CF), there is a current focus in the CF community on developing and evaluating endpoints for clinical trials, especially in the early stages of CF lung disease (reviewed in [1]). The European Cystic Fibrosis Society Clinical Trial Network (ECFS-CTN) has established a Standardization Committee to undertake a rigorous evaluation of promising outcome measures with regard to use in multicentre clinical trials in young children with CF.

CF lung disease starts in early life and associates airway remodelling to bacterial infection and inflammation, resulting in an obstructive ventilatory defect which can be observed by lung function testing. Therefore, sensitive tools are needed to evaluate respiratory status in infants and guide interventions to improve respiratory outcome. Previous multicentre early intervention clinical trials have used ventilatory parameters as a secondary endpoint e.g. the raised volume-rapid thoracic compression (RVRTC) technique, or lung clearance index (LCI) [2–5]. RVRTC appeared to be a promising tool to monitor early lung disease in CF infants.

Pulmonary function test performance is particularly difficult from 0 to 3 years due to the lack of cooperation of the child. The RVRTC technique allows infant lungs to be inflated to near vital capacity (VC) by applying an inspiratory pressure to the airways through a face mask during inspiration followed by a rapid thoracic compression (RVRTC) manoeuvre applied through a jacket, at the end of the inflated inspiration (so called 'pump up and squeeze' technique). It measures volume and flow measurements during compression, such as: a) Forced expired volume in 0.4 or 0.5 s ($FEV_{0.4}$, $FEV_{0.5}$), b) Mean forced expiratory flow between 25 and 75% of FVC ($FEF_{25–75}$) and c) Forced expiratory flow at 75 or 50% of FVC (FEF_{75}, FEF_{50}) similar to spirometric forced flow-volume loops in older children [6,7].

In the early 2000s, following a joint effort by the American and European Respiratory Societies, raised volume forced expiration measurements were standardized [8] and implemented in centres around the world [8–11]. The current manuscript summarises information on the RVRTC technique as an endpoint of infant pulmonary function in CF, states recommendations by the ECFS-CTN to achieve standardization of this technique and lists further studies needed.

2. Methods

An exhaustive literature search was conducted in MEDLINE, Allied and Complementary Medicine (AMED) and Embase using the following search criteria: (infant pulmonary function) OR (infant respiratory function) OR (raised volume rapid thoracic compression) OR (raised volume rapid thoraco-abdominal compression) AND (cystic fibrosis). The search was not limited by year of publication. A bibliography search was also conducted of all included articles and relevant reviews. This search identified 25 papers from 1985 to present. The papers' abstracts were checked in order to verify that RVRTC results were indeed reported. Five papers were rejected because they did not report results in infants with CF. Finally, 20 papers were selected and are presented in Appendix 1. We repeated the procedure twice and obtained the same result.

To describe the clinimetric properties, data were extracted and tabulated for repeatability, validity and correlation with other outcome measures, responsiveness and reference values. Definitions of each clinimetric property have been presented in a previous paper [12].

To evaluate feasibility, data on proportion of successful attempts and reasons for excluding tests were tabulated. An expert panel further discussed the following topics until they reached consensus on each: risk involved, cost, ease of performance, equipment and space needed, ease of administration, time to administer, and applicable age group. Specific advantages and limitations were also listed.

Narrative answers to 4 key questions were discussed by the expert panel during several face to face meetings (see below):

- Question 1: Does infant RVRTC have the potential to become a surrogate outcome?
- Question 2: For what kind of therapeutic trial is the infant RVRTC technique appropriate? (therapeutic aim; phase of trial, target population, number of patients involved, number of sites involved)
- Question 3: Within what timeline can change be expected and what treatment effect can be considered clinically significant?
- Question 4: What studies are the most needed to further define infant RVRTC in CF patients and its potential to be a surrogate marker?

After preparatory work over a period of 6 months based on an exhaustive literature search, each co-author proposed a table predefined by the groups during several oral sessions (November 17 and 18, 2010; June 9, 2011). The group reviewed each table until consensus was obtained with regards to accuracy, exhaustiveness and clarity for a naive reader. After a final update of the table, one oral session was organized (23 January 2013) allowing the group to freely comment on each table in regard to the 4 key questions. Finally, the response to each of the 4 key questions was written by one different co-author and proposed to the group. The group reviewed each response until consensus was achieved. The manuscript was developed by the core writing team (SM, LK, IS, PR) and reviewed by the group for final validation.

3. Results

3.1. Clinimetric properties of infant RVRTC

3.1.1. Repeatability

Within test repeatability of RVRTC is an important prerequisite for test acceptability and analysis as defined by ATS/ERS guidelines [8]. Flow-volume curves are deemed acceptable when the within-session coefficient of variation (CV) of forced volume and flow (defined as the ratio between standard deviation and the mean) is below 10%. CV is calculated on the two best curves, defined as those having the highest sum of FVC and $FEV_{0.4/0.5}$ or FEF_{25-75}. The CV of different RVRTC parameters was reported in a few studies and yielded similar results. The CV was lowest for $FEV_{0.5}$ (2 to 6%) [13–16] while the CV for FEF at different lung volumes was around 10% [13–15]. A potential source of bias exists regarding those results since data collection immediately ceases once criteria for acceptability have been achieved. Thus, most studies do not really report real repeatability but present data on a selected subset of tests.

Data on between-sessions repeatability are scarce. Davis et al. assessed RVRTC reproducibility between 2 sessions one month apart in clinically stable patients (Table S1, online supplementary data) [17]. Good repeatability and high intra-class correlation index were reported when the parameters were expressed as raw values. However, when expressed as Z-scores, the difference in $FEV_{0.5}$ between 2 sessions was ≥ 1 Z-score in one third of the patients, albeit the difference remained below 1.96 Z-score in all except one infant.

3.1.2. Discriminate validity

3.1.2.1. CF versus healthy infants. Six cross-sectional [15,18–22] and one longitudinal study [23] using RVRTC measurements document that RVRTC parameters such as FVC, $FEV_{0.5}$, FEF_{75} and FEF_{25-75} can discriminate patients with CF from healthy controls (Table 1). Five studies included infants younger than 6 months of age. Only 1 did not observe any differences between CF infants and their healthy counterparts in regard to FVC, $FEV_{0.5}$ and FEF_{75} [20,21]. The 2 more recent studies reported a significant difference, even before 3 months of age [18,23]. Interestingly, the only longitudinal study documented RVRTC differences between infants with CF and controls at age 3 months, that were no longer apparent at one year of age [23]. Indeed, RVRTC parameters improved between 3 months and one year of age in infants with CF, in contradiction to the decrease observed previously in infants with CF after clinical diagnosis [24]. One explanation could be that CF infants after NBS are healthier or still have some degree of reversible respiratory disease. This important recent observation needs to be confirmed by further studies before considering RVRTC parameters as primary end points for phase III trials.

Table 1
Discriminate validity of RVRTC parameters between patients with cystic fibrosis (CF) and healthy infants.

First Author	CF infants		Non-CF infants		FVC	$FEV_{0.5}$	FEF_{75}	FEF_{25-75}
	N and CF diagnosis	Age (months)	N	Age (months)	Statistical test used: means comparison between CF and non-CF using unpaired-*t* test			
In cross sectional studies RVRTC can differentiate infants with CF and healthy infants:								
Result expressed as difference in Z-score between CF and non-CF: mean [95% CI] OR mean ± SD								
Hoo [18]	71	2.6 ± 0.5	54	2.8 ± 0.4	−0.6 [−0.92/−0.28]**	−0.92 [−1.29/−0.56]**	−0.53 [−0.95/−0.11] *	−0.66 [−1.10/−0.21]*
	100% NBS							
Lum [19]	66	12.3 ± 6.1	54	11.8 ± 5.8	−0.97 ± 1.18 **	−1.18 ± 1.35 **	NR	−0.76 ± 1.42 **
	NR							
Linnane [20]	68	13.6	49	9.4	After 6 months of age (NS before 6 months of age)			NR
	100% NBS	[1.4–30.1]		[1.2–27.2]	−0.62 [−1.11/−0.18]*	−1.15 [−1.57/−0.72]**	−1.09 [−1.55/0.62]**	
Lum [15]	39	9.0 ± 0.5	21	9.1 ± 0.3	−1.1 [−1.6/−0.6] **	−1.7 [−2.3/−1.1] **	−1.4 [−2.1/−0.8] **	−1.5 [−2.2/−0.9] **
	100% CD							
Ranganathan [21]	37	6.5	33	0.39	−1.57 [−2.2/−0.9] **	−1.6 [−2.7/−1.1] **	−1.42 [−1.7/−0.28] **	NR
	100% CD	[3.8–9.9]		[1.3–2.0]				
	37	13.6	33	7.7	−1.1 [−1.8/−0.5] **	−1.9 [−2.5/−0.5] **	−1.2 [−1.9/−0.56] **	NR
	100% CD	[11.1–15.9]		[6.5–11.5]				
Kozlowska [22]	48	7.2	33	2.4 [1.1–23]	−1.8 ± 1.4 **	−2.0 ± 1.8 **	NR	−1.4 ± 1.9 **
	100% CD	[1.7–21.2]						
One longitudinal study documents discriminate validity of RVRTC at age 3 months but not at age 1 year between infants with CF and healthy controls:								
Nguyen [23]	72	T1: 2.6 ± 0.5 T2: 12 ± 1.2	44		FVC		$FEV_{0.5}$	FEF_{75}
	100% NBS				CF	nCF	CF nCF	CF nCF
				T1:2.8 ± 0.5 T2: 12.3 ± 1	−0,50 (.03)	0.23 (0.67)	−1.23 (1.07) −0.16 (0.76)	−0.76 (1.25) −0.07 (0.96)
					−0.43 (1.16)	0.23 (0.94)	−0.41 (1.03) 0.12 (0.92)	−0.09 (0.93) 0.09 (0.91)
				Difference [a]	0.08 (−0.29 to .45)^{NS}		0.59 (0.18 to 0.99)*	0.63 (0.12 to 1.14)*

Age: median [range] or mean ± standard deviation.
*p < 0.05, **p < 0.001; unpaired *t*-test.
NS: nonsignificant.
NBS: newborn screening; CD: clinically diagnosed.
[a] Results expressed as difference between absolute changes in Z-scores between CF and non-CF infants (nCF) between 3 months (T1) and one year (T2) [(CF Z-scores T2–T1)-(non-CF Z-scores T2–T1)].

Table 2
Convergent validity: association between RVRTC parameters and other variables assessing respiratory status in young children with cystic fibrosis (CF).

First author	N	Age (month)	Outcome variables	Main result	Statistic
Markers of inflammation					
Cross sectional studies which evaluated association between inflammatory markers in bronchoalveolar lavage and RVRTC parameters					
Peterson-Carmichael [28]	16	19.8 [4.1–38.4]	$FEV_{0.5\ s}$ vs MMP-2 or % NC or pathogen density	NS	Spearman correlation.
			FEF_{75} vs % NC	$r = -0.67$**	
			FEF_{25-75} vs %NC	$r = -0.63$**	
			FEF_{75} vs pathogen density	$r = -0.70$**	
			FEF_{25-75} vs pathogen density	$r = -0.70$*	
			FEF_{75} vs MMP-2	$r = -0.74$*	
			FEF_{25-75} vs MMP-2	$r = -0.78$**	
Nixon [26]	54	<36	FEVs vs pathogen density, IL8, NE	NS	General estimating equations
Linnane [20]	68	13.6 [1.4–30.1]	$FEV_{0.5\ s}$ vs pathogen density, IL8, NE, %NC FVC vs pathogen density, IL8, NE, % NC FEF_{75} vs pathogen density, IL8, NE, %NC	NS	Multiple linear regression
Cross-sectional studies which evaluated association between exhaled breath condensate and RVRTC parameters					
Patel [29]	11	25.2 ± 10.8	FVC vs AMP/ado	$r^2 = -0.72$*	Pearson correlation
			$FEV_{0.5\ s}$ vs AMP/ado	$r^2 = -0.9$**	
			FEF_{25-75}, FEF_{75} vs AMP/ado	NS	
Longitudinal study which evaluated association between neutrophil elastase in bronchoalveolar lavage and RVRTC parameters decline					
Pillarisetti [24]	37	T1: 4.6 [3.5–5.3] T2: 12.8 [11.7–13.8] T3: 23.9 [23.7–24.9]	ΔZ-score of FVC for each NE level doubling	−0.55 [−0.82/−0.27]***	General estimating equations
			ΔZ-score of FVC for each NC, IL8, IL1-β or, TCC levels doubling	NS	
			ΔZ-score of $FEV_{0.5\ s}$ for each NE level doubling	−0.46 [−0.77/−0.16]***	
			ΔZ-score of $FEV_{0.5\ s}$ for each when NC,IL8,IL1-β or, TCC levels doubling	NS	
			ΔZ-score of FEF75 for each NE, NC,IL8,IL1-β or TCC levels doubling	NS	
Airway colonisation					
Longitudinal study which evaluated association between bacterial status in bronchoalveolar lavage and RVRTC parameters decline over time					
Pillarisetti [24]	37	T1: 4.6 [3.5–5.3] T2: 12.8 [11.7–13.8] T3: 23.9 [23.7–24.9]	Difference in ΔZ-score of $FEV_{0.5}$ between infected and non infected with SA	−0.25/10 wk [−0.45/−0.04] ***	General estimating equations
			Difference in ΔZ-score of $FEV_{0.5\ s}$ between infected and non infected with PA	−0.38/10 wk [−0.71/−0.06] ***	
			Difference in ΔZ-score of FVC between infected and infected with SA or PA	NS NS	
			Difference in ΔZ-score of FEF_{75} between infected and non infected with SA or PA		
Brumback [30]	45	3 to 9 visits from 12.8 to preschool age	% of $FEV_{0.5\ s}$ decrease in infected compared to non infected with PA	−5.1% [−9.9/−0.01]*	Mixed effect model analysis
			% of FEF_{25-75} decrease in infected compared to non infected with PA	−16.4% [−24.9/−7.0]*	
			% of $FEV_{0.5\ s}$ decrease in infected compared to non infected with SA or HI	NS	
			% of FEF_{25-75} decrease in infected compared to non infected with SA or HI	NS	
			% of FVC decrease in infected compared to non infected with HI	−4% [−7.7/−1.1]*	
			% of FVC decrease in infected compared to non infected with PA or SA	NS	
Lung clearance index					
Cross sectional study which evaluated association between RVRTC and lung clearance index					
Hoo [18]	71	2.6 ± 0.5	$FEV_{0.5\ s}$ vs LCI	NS	Pearson correlations
Longitudinal study which evaluated association between RVRTC and lung clearance index					
Nguyen [23]	72	T1: 2.6 ± 0.5 T2: 12 ± 1.2	$FEV_{0.5\ s}$ vs LCI	NS	Pearson correlations
Imaging					
Cross sectional study which evaluated association between RVRTC and structural high resolution computed tomography measurements					
Martinez [16]	11	4.0 [4.1–38.4]	$FEV_{0.5}$ vs ratio wall area to lumen area	$r^2 = 0.66$***	NR
			FEF_{50} vs ratio wall area to lumen area	$r^2 = 0.41$***	
			FEF_{75} vs ratio wall area to lumen area	$r^2 = 0.40$***	

Table 2 (*continued*)

First author	N	Age (month)	Outcome variables	Main result	Statistic
Imaging					
Longitudinal study which evaluated association between RVRTC and chest X-ray scores decline					
Rosenfeld [31]	100	T1: 14.0 ± 6.2 T2: T1 + 6 months T3: T1 + 12 months	$\Delta FEV_{0.5}$ vs Δ Brasfield or Wisconsin score	NS	Mixed effects models
			ΔFEF_{75} vs Δ Brasfield or Wisconsin score	NS	

Age: median (range) or mean ± standard deviation.
*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$; and NS: not significant.
N: number of subjects.
Abbreviations used: T1: first visit; T2: second visit; T3: third visit; Ado: adenosine; AMP: adenosine monophosphate; FEFx: forced expiratory flow at x% of exhaled vital capacity; FEF_{25-75}: Mean forced expiratory flow between 25 and 75% of forced vital capacity; FEVx: forced expiratory volume in x seconds; FVC: forced vital capacity; MMP: matrix metalloproteinase; %NC: percentage of neutrophil count, NE: neutrophil elastase; NR: not reported; TCC = total cell count; Δ: change; SA: *Staphylococcus aureus*; PA: *Pseudomonas aeruginosa*; and HI: *Haemophilus Influenzae*.

In all these studies, $FEV_{0.5}$ demonstrated a larger discriminative power with an average Z-score difference of 1 to 2 between CF and controls.

Interestingly, one study provides evidence that $FEV_{0.5}$ in infancy corresponds to FEF_{75} and FEF_{25-75} measured at preschool age [22]. This is may be explained by developmental changes. Indeed, postnatal lung growth is faster than airway calibre change which explains that the same flows reflect different parts of the flow volume curve at different ages.

3.1.2.2. Discrimination between subsets of disease severity. Several attempts have been made to correlate RVRTC parameters to clinical phenotype, *CFTR* (Cystic Fibrosis Transmembrane Conductance Regulator) genotypes, CF respiratory symptom severity, and bacterial airway colonisation status assessed by bronchoalveolar lavage (BAL) [18,21,25,26] or cough swab [2]. There was no correlation with *CFTR* genotypes. However, $FEV_{0.5}$ could discriminate between patients with a clinical history of physician-diagnosed wheeze [27] ($p = 0{,}02$), respiratory symptoms or positive cough swab [18], while FEF_{75} discriminated infants with and without parent reported cough [5].

3.1.3. Convergent validity

Table 2 presents the association of RVRTC measures with other outcome measures in infants with CF.

3.1.3.1. With inflammatory markers. Cross-sectional studies have shown correlations between RVRTC parameters and inflammatory markers (1) in plasma (adenosine monophosphate, adenosine), (2) BAL (interleukins 8 and 1, matrix metalloproteinase-2, neutrophils counts, neutrophil elastase), or (3) exhaled breath [20,24,26,28,29]. Importantly, a 2-fold increase in neutrophil elastase levels in BAL in the first 2 years of life was associated with a decrease in FVC and $FEV_{0.5}$ of respectively −0.55 and −0.46 Z-score [24]. However, it should be noted that 2 studies [28,29] present small sample size and thus are likely to be highly susceptible to type 1 errors and insufficient power and should not be given the same weight as others with larger sample size.

3.1.3.2. With airway colonisation by pathogens. Two longitudinal studies during infancy [24] and infancy to preschool age [30] have shown that recent *Pseudomonas aeruginosa* or *Staphylococcus aureus* airway colonisation was negatively associated with $FEF_{0.5}$ and/or FEF_{25-75} levels.

3.1.3.3. With multiple breath washout index. In infants with CF diagnosed by NBS, no correlation was found between LCI measured with sulfur hexafluoride and $FEV_{0.5}$ [18]. Moreover, although both parameters measured at 3 months of age were valuable predictors of the value at one year, $FEV_{0.5}$ was not significantly associated with LCI neither at 3 months nor at one year [23].

3.1.3.4. With imaging data. A large multicentre prospective study did not find any correlation between $FEV_{0.5}$ and chest X-ray scores (Brasfield and Wisconsin scores) in infants with CF younger than 24 months at study entry [31]. When using high resolution chest CT, a small size (N = 11) cross-sectional study did report a significant correlation between FEF_{50}, $FEV_{0.5}$ and FEF_{75} and airway remodelling/thickening as assessed by bronchial wall area to lumen area ratio [16].

3.1.4. Predictive validity

One longitudinal study evaluated the capacity of early RVRTC parameters to predict later airway obstruction [32]. In this study, FEF_{50} measured at a mean age of 7.4 months (0.53 to 31.2 months) was found to be the only RVRTC parameter that predicted low FEF_{25-75} and FEF_{50} at the age of 6 to 8 years.

3.1.5. Responsiveness

Only two studies have evaluated the responsiveness of RVRTC parameters to a therapeutic intervention (Table S2, online supplementary data).

A retrospective study in 11 CF infants showed a statistically significant improvement of FVC, $FEV_{0.5}$, FEF_{75} and FEF_{25-75} after intravenous antibiotic therapy for acute pulmonary exacerbation [33]. This result mirrors the correlation found between airway bacterial infection and lower RVRTC parameters [24,30]. This study should however be interpreted with caution because of the small sample size and the fact that the infants were clinically unwell. Indeed, future interventional studies should have higher patient numbers and most importantly, for reasons of safety and accuracy of results, should preferably

be conducted in infants who are clinically stable both at baseline and after intervention.

Hypertonic saline nebulisation significantly improved $FEV_{0.5}$ in a recent multicentre one-year intervention study conducted in infants and toddlers [25]. However, due to the small sample size and the lack of a power calculation to specifically answer the question of IPFT (infant pulmonary function testing) alterations after intervention, the positive findings may contain a type 1 error and the clinical significance remains unclear.

3.1.6. RVRTC reference values

Table S3, online supplementary data, presents reference equations for RVRTC parameters in healthy subjects. It must be highlighted that some reference equations come from studies using custom-made devices [34,35] and were already used for RVRTC standardization well before ATS/ERS guidelines [8]. It should be emphasised that some equations were obtained using an inflation pressure of 20 cm of water [20], while many others used 30 cm of water [19,34–36] (see Appendix 1).

3.1.7. Equipment and method used to obtain RVRTC data in infants with CF

Results of RVRTC parameters (FVC, $FEF_{0.5}$, FEF_{75} and FEF_{25-75}) in CF infants are reported in Table S4, Online Supplementary data. The results differ considerably between studies. These discrepancies can be related either to the type of patient's diagnosis (clinically diagnosed or newborn screened), clinical status and symptoms, the age of the infants tested, the device used, the protocol used including the insufflation pressure, training and experience of the investigator and finally to the reference values used to express infants' results.

Indeed, many authors used the reference values from historical [5,17,19,24,27,28,32,37] rather than contemporaneous control groups [20,22,23]. Some others have used these reference values but adjusted with an equipment-correcting factor specific to the Jaeger device [18,23,25].

It should also be noted that the inflation pressures used were 20 or 30 cm of water, making the comparability of the results of these studies difficult and highlighting the need to take this into account in future studies. Indeed, studies which proposed their own reference data derived from application of thoraco-abdominal pressure at 20 cm H_20 [20] rather than 30 cm H_20, may not be transferable to future studies which are based on 30 cm H_20 inflation pressure.

Importantly, the characteristics of the control population influence the results when expressed as Z-scores. Thus, the use of historical controls evaluated on different equipment [20,24] rather than contemporary controls with the same equipment or the use of lower inflation pressure before RVRTC [20] may bias interpretation. Finally, both the training of the operator as well as expertise at the centre are of utmost importance. This is highlighted in Table S4, where the three studies which present the most similar RVRTC data are provided by the same reference centre using the same device and the same reference data [18,19,23].

3.1.8. Feasibility

3.1.8.1. Performance. Success rate ranged from 62 to 96% according to the studies (Table 3). Non-acceptable data were related either to non-achievement of ATS/ERS acceptability requirements or practical issues (e.g. inability to obtain quiet sleep in large majority). Overall RVRTC requires high technical skills, sustained training and frequent RVRTC performance using standardized operating procedures in order to ensure good quality data collection. It may take 6 months to 1 year of regular performance before users are able to perform technically acceptable tests. Tests should meet numerous acceptability criteria that are difficult to be consistently obtained in less experienced centres. This was studied in a multicentre study in which 7 out of 10 centres were naive to RVRTC. Overall, acceptability rates were significantly higher in the experienced sites, (85%–94%) [17,23] vs 59% ($p < 0.0001$) at the inexperienced sites [17]. Moreover, longitudinal studies [17,25] clearly show that feasibility is reduced when repeated RVRTC tests are required (this ranges from 60% to 92% success rate versus 84 and 96% in cross sectional studies [13–15,18,23,26]). This should be taken into consideration when setting up studies (number of time-points and the potential number of experienced centres available).

3.1.8.2. Risk. Sedation with oral chloral hydrate is used for infant lung function testing. A recent study of 100 infants who completed 342 infant lung function procedures revealed a total of 44 adverse events amongst 26 participants, possibly related to study procedures [17]. The most common adverse event was emesis; one subject experienced a serious adverse event i.e. tachycardia, wheezing and hypoxaemia leading to an overnight hospitalisation. This subject had an early upper respiratory infection with rhinorrhoea that at the time of the visit was felt to be allergy-related. In retrospect, this might explain this adverse event [17]. Given the sedation risk, a minimum requirement is the presence of two well-trained technicians during the test and a physician available nearby. In some centres nurses or doctors trained in sedation, monitoring and resuscitation are required to perform infant pulmonary function testing.

3.1.8.3. Cost. The cost of equipment to perform the RVRTC is high, around 60,000 Euros in Europe. Additional costs include consumables (facemasks, filters, putty, chloral hydrate), equipment servicing and technical support, plus a high personnel cost. However, a precise cost estimate is difficult. Ideally, it should reflect the true cost of performing the RVRTC in one patient. This includes capital costs + salaries of staff who need 6–12 months training, and taking into account that by the time a test has been scheduled (and rescheduled), equipment calibrated, testing performed, results analysed and report produced, each test probably equates to a minimum of 0.5 day for 2 trained staff. From this statement, an estimate of 1500 to 2000 Euros per test is not unrealistic.

3.1.8.4. Time for procedure and space. The total time required to perform the RVRTC procedure is between 2 and

Table 3
Feasibility of RVRTC in patients with CF is better in cross-sectional than in longitudinal studies.

First author [ref]	N	Age (months)	Measures (n=)/test	Number of test/infant (Δt = time between tests)	% of acceptable measurements for RVRTC tests	% of non acceptable data % of non obtained data
Rosenfeld [25]	73	4 to 16	NR	2 (Δt = 48 wk)	62%	38% total
Davis [17]	100 (at T0)	14 ± 6.2	NR	T0: 1	72%	16%
	91 (at T1)			T1: 2 (Δt = T0 + 6 months)	58%	12%
	77 (at T2)			T2: 2 (Δt = T0 + 12 months)	60%	
	63 (at T3)			T3: 4 (Δt = T0 + 24 months)	40%	
Lum [15]	42	9.0 ± 0.5	At least 3	1	86%	1.4% 11.5%
Martinez [16]	13	17.2 [8–33]	3	1	84.6%	0% 15.4%
Ranganathan [40]	47	1.4 to 21.4	At least 2	1	89.3%	0% 10.7%
Pillarisetti [24]	45	3 visits at 4.6, 12.8 and 23.9[a]	At least 2	2 to 3 (Δt = 24 months)	82%	2% 16%
Nixon [26]	41	<36	At least 3	1	88%	12% 0%
Subbarao [13]	13	18.6 ± 7.2	At least 2	1	84%	0% 16%
Hoo [18]	71	2.6 ± 0.5	At least 3	1	96%	4% total
Brumback [30]	45	12.8 ± 6.2	At least 2	3 (Δt = 6 months) + 1 (Δt = 1 month)	73%	NR
Nguyen [23]	72	2.6 ± 0.5	At least 2	2 (Δt = 10 months)	92%	NR

N: number of subjects.
[a] Median age, NR: not reported.

3 h per patient (including sedation and recovery after the procedure). The RVRTC technique takes approximately 15 to 20 min to perform. Moreover, we should also consider the burden on parental time and the susceptibility of this population to frequent respiratory tract infections in the first 2 years of life which often delays, postpones or even cancels the exam, and increases the time-consuming characteristic of this examination.

Furthermore, the equipment requires a dedicated space. Infant lung function equipment is not portable and the baby body box is large. The typical amount of space needed is a minimum of 20 m^2.

4. Discussion

RVRTC measurements provide parameters potentially useful for the follow up of lung function of CF infants. The availability of commercial devices facilitates the spread of this technique. It cannot however be used as a primary outcome because intra-individual variability is large even when clinical status appears to be stable [17].

A possible way to limit this variability would be to perform RVRTC repeatedly and express results as a decline of lung function parameter ($FEV_{0.5}$ decline) over time, as is routinely done for older patients with FEV_1. As shown in Table S4, only two studies from expert teams have evaluated the changes in RVRTC parameters over time. These results emphasise that, as in adults, FEV rate of decline is highly variable. Indeed, the first study [24] showed a decrease over time during the first 2 years of $FEV_{0.5}$, while the second [23] in infants diagnosed after newborn screening, showed a lung function improvement over time and a correlation between pulmonary function tests at 3 months and at 1 year.

Reference values are not interchangeable if they are obtained with different devices, and the variability of RVRTC reference values obtained on specific commercially available devices is clearly an issue that limits RVRTC usefulness in both research and clinical settings. One way to solve this issue might be to follow the proposal of Lum et al. [19] who measure with specific commercial equipment (MasterScreen™ BabyBody Plethysmograph, Hoechberg, Germany) but use an equipment correction factor to reference equations obtained with custom-made devices [37]. The second more recent longitudinal study [23], which expressed $FEV_{0.5}$ change as adjusted Z-score according to Lum et al. [19], observed an improvement of $FEV_{0.5}$ over time during the first year, which may considerably limit the use of RVRTC outcomes over time. It should however be pointed out that this correcting factor which limits the risk of overestimation of the lung disease has been validated in infants whose height is over 68 cm. Indeed, the adjusted Z-score for $FEV_{0.5}$ is, according to Lum et al. [19]: $\text{Z-score}_{\text{Jones}} + 0.058 * \text{length} - 3.83$ where $\text{Z-score}_{\text{Jones}}$ is the result expressed in Z-score according to a historical control subject with a noncommercially available device [37]. According to this equation, the adjusted Z-score for $FEV_{0.5}$ becomes lower than the Z-score from the historical control subject [37] in infants smaller than 68 cm and higher in taller infants. Thus, in growing infants, this equipment correcting factor with a cut off at 68 cm may also partly explain discrepancies between longitudinal studies [24] that express results in delta Z-scores over time according to Jones equation [37] and more recent studies that express results in delta adjusted-Z-scores [23].

It is therefore obvious, in regard to these 2 previous longitudinal studies that more data are necessary to interpret follow-up data of RVRTC measurements in infants with CF diagnosed after NBS.

5. The "four key questions"

5.1. Question 1: does infant pulmonary function have the potential to become a surrogate outcome?

Amongst all RVRTC parameters, $FEV_{0.5}$ displays the better clinimetric properties for surrogate outcome such as: a) repeatability, b) discriminative validity, c) association with other outcome measures, d) predictive validity and e) responsiveness.

However, several considerations limit use of RVRTC as a surrogate marker in clinical trials in CF infants, especially in phase III studies. First, there is an important variability between sessions [9] which considerably limits the RVRTC discriminate validity in regard to any therapeutic effect. Second, there is a critical need for more RVRTC reference values obtained with commercially available devices. Finally, phase III clinical trials require large sample sizes in multicentre studies, where each centre should be able to express their result in Z-scores appropriate for the equipment used. This however requires harmonization between the centres. Implementation of ECFS-CTN Standard Operating Procedures (SOPs) in Europe and Therapeutic Diagnostic Network SOPs in USA, in addition to training and certification of highly skilled personnel in the centres according to these SOPs and quality control assessment should help to achieve high quality data, reduce result variability and better delineate indication of RVRTC parameters in large multicentre trials. Moreover, test over-reading by an expert core RVRTC centre should also be set-up in multicentre studies in order to optimize data quality.

Considering all the above-mentioned points/limitations, the ECFS-CTN highlights the need to achieve universal standardization of this technique to promote RVRTC to a surrogate outcome.

5.2. Question 2: for what kind of therapeutic trial is the RVRTC technique appropriate? (therapeutic aim; phase of trial, target population, number of patients involved, number of sites involved)

RVRTC has been used successfully in a limited number of interventional clinical trials [13,38] including a mono-centre trial assessing treatment with intravenous antibiotics [36] and in a subset of patients in selected sites of a phase 3 trial evaluating efficacy of hypertonic saline [25,33].

An important unsolved question is the number of infants to be enrolled. This should take into account the power calculation, the success rate of repeated testing and the parental consent rate. Using data from a recent longitudinal study, comparing infants with CF and healthy controls [23] per group, 85 infants with acceptable measures would be required to detect a small difference (i.e., equivalent to 0.5 Z-scores). Interestingly this number could be considerably decreased (22 infants with acceptable measure per arm) to detect treatment effect equivalent to 1 Z-scores or if recruitment is limited to a 'high-risk group' (i.e., abnormal lung function testing at 3 months of age) [23]. Recently, the feasibility of recruiting infants following a NBS diagnosis of CF for a study involving RVRTC at both 3 and 12 months of age was reported by the London Cystic Fibrosis Collaboration group [39] as 86% of families. This is close to the one reported by the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF) group. Based on their results, it was calculated that for 45 acceptable measures at 2 time points, 78 patients need to be enrolled.

In light of the present knowledge, the Standardization Committee of the European Clinical Trial Network proposes that RVRTC can be used as primary endpoint for phase I or II trials when a large treatment benefit is anticipated or in observational studies in infants. For phase III studies, it may be considered as a secondary endpoint in large multicentre trials if rigorous standardization of this technique is implemented.

5.3. Question 3: within what timeline can change be expected and what treatment effect can be considered clinically significant?

No study has reported a link between improvement in $FEV_{0.5}$ after a therapeutic intervention and change in any primary clinical endpoint in infants and toddlers. It does not allow definition of a threshold value for $FEV_{0.5}$ increase that can be considered as clinically significant nor a timeline.

5.4. Question 4: what are the most needed studies to further define infant pulmonary function in CF patients and its potential to become a surrogate marker?

ECFS-CTN proposes that there is a need to conduct studies to develop appropriate reference data and knowledge of within- and between-test reproducibility, with the aim that the RVRTC technique can become a surrogate marker. It is both indispensable for implementation in future clinical trials but also urgent in regard to the question whether these tests can improve the clinical management of infants with CF and should be recommended in the follow-up of infants with CF.

There is the need to establish healthy infants' global reference values in relation to the commercial devices and to compare the clinimetric properties and feasibility of the different set-ups available. This study must be done in collaboration with manufacturers. It will help to develop inter-institutional networking for sharing data, implementation of regular quality control and identification of expert centres.

In CF infants, we need multicenter prospective long-term follow-up studies, to describe the evolution of RVRTC outcomes under current standard management in infants diagnosed after NBS. Such studies should also incorporate other relevant endpoint outcomes to investigate correlations with RVRTC parameters (e.g. respiratory symptoms, therapeutic outcomes, multiple breath washout indices, plasma or BAL infectious and inflammatory biomarkers, volume-controlled chest CT). The second aim of these studies will be to evaluate short-term repeatability of RVRTC measurements to better

define the "normal" variability. However, this kind of evaluation may raise ethical concerns due to the need for repeated sedation over short between-session time frames in order to limit variability due to lung disease progression.

6. Conclusion

This document provides a systematic review of the clinimetric properties of RVRTC. The ECFS-CTN does not recommend RVRTC parameters as a primary outcome in clinical trials in infants with CF but highlights available data on repeatability, discriminative properties and correlation with other parameters expressing lung disease status. The ECFS-CTN Respiratory Function Group considers that RVRTC cannot be used as a primary outcome in clinical trials in infants with CF before universal standardization of this measurement is achieved and implementation of inter-institutional networking is in place, and advises its use currently in phase I/II trials and as a secondary endpoint in phase III studies.

The ECFS-CTN Respiratory Function Group also emphasises the urgent need to develop multicentre longitudinal studies in healthy and CF infants, using the same commercially available devices to develop adapted reference values. This will enable evaluation of short term RVRTC variability and therefore better describe the natural history of infant lung function in CF.

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Appendix 1. studies identified, equipment used

Study #	First author	Equipment used	Equipment commercially available?	Historical or contemporary controls
1	Hoo [18]	Jaeger	Yes	Contemporary
2	Lum [15]	Jaeger	Yes	Contemporary
3	Linnane [20]	Home made	N/A	Contemporary
4	Lum [19]	Jaeger	Yes	Historical
5	Ranganathan [21]	PNT + DPT	N/A	Contemporary
6	Nguyen [23]	Jaeger	Yes	Contemporary
7	Kozlowska [22]	Jaeger	Yes	Contemporary
8	Peterson-Carmichael [28]	nSpire Health, Inc.	N/A	Historical
9	Nixon [26]	NR	N/A	Contemporary
10	Patel [29]	nSpire Health, Inc.	No	N/A
11	Pillarisetti [24]	Home made	N/A	N/A
12	Brumback [30]	nSpire Health, Inc.	No	N/A
13	Rosenfeld [38]	nSpire Health, Inc.	No	Historical
14	Davis [17]	nSpire Health Inc.	No	Historical
15	Martinez [16]	NR	NR	Contemporary
16	Subbarao [13]	NR	NR	N/A
17	Pittman [33]	nSpire Health Inc.	No	N/A
18	Castile [35]	PNT + DPT[a]	N/A	N/A
19	Jones [34]	PNT + DPT[b]	N/A	N/A
20	Harrison [32]	Sensor Medics	No	N/A

NR: not reported.
N/A: not adapted.
Jaeger: Masterscreen BabyBody System (CareFusion, Hoechberg, Germany).
SensorMedics: Paediatric Pulmonary Unit 2600 (SensorMedics, Anaheim, CA, USA). This device is no longer available.
nSpire Infant Pulmonary Function Lab (nSpire, Inc., Longmont, CO, USA). This device is no longer available.
PNT + DPT[a]: Pneumotachometer model 3700 (Hans Rudolph, Kansas City, MO, USA) + differential pressure transducer (Validyne MP45, Northridge, CA, USA).
PNT + DPT[b]: Pneumotachometer model 3700 (Hans Rudolph, Kansas City, MO, USA) + differential pressure transducer (Validyne MP45-871, Northridge, CA, USA).

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