2 PROTOCOL SYNOPSIS

INFORMATION TYPE	SUMMARY DETAILS
Short study title	RELIEF
Study title	**Re**stricted versus **li**b**e**ral **f**luid intake for prevention of bronchopulmonary dysplasia – **RELIEF trial**. A cluster-randomised multiple period cross-over trial.
Study design	Pragmatic, registry-linked, multicentre, open-label, cluster-randomised, multiple period, cross-over, effectiveness trial performed in Swiss neonatal intensive care units (NICUs).
Study population	Preterm infants born < 30 weeks GA, from day 8 of life, admitted to participating NICUs.
Setting	NICUs of all nine level 3 perinatal centres in Switzerland.
Primary effectiveness objective	To determine the effectiveness of restricted vs. liberal fluid intake in reducing the incidence of BPD at 36 weeks postmenstrual age or prior death in preterm infants.
Secondary objectives	To determine the effect of restricted vs. liberal fluid intake on major complications of prematurity, feeding tolerance, growth, fluid status, use of diuretics, use of corticosteroids, and extent of respiratory support in the NICU.
Exploratory objectives	To determine the effect of restricted vs. liberal fluid intake on exploratory outcomes at 6-12 months post-term, including growth, respiratory outcomes following discharge from the NICU, and visits to the emergency department. To determine the effect of restricted vs. liberal fluid intake on exploratory outcomes at 18-24 months post-term, including growth and neurodevelopment based on parental PARCA-R questionnaire.
Intervention	Fluid restriction strategy (fluid target 135 ±5 mL/kg/d) in line with international best practice recommendations on nutrition. All other care is provided based on local practice.
Comparison	Liberal fluid intake strategy (fluid target 165 ± 5 mL/kg/d) in line with international best practice recommendations on nutrition. All other care is provided based on local practice.
Primary study hypothesis	Restricted fluid intake compared to liberal fluid intake reduces the incidence of BPD at 36 weeks postmenstrual age or prior death.
Secondary study hypotheses	Restricted fluid intake compared to liberal fluid intake reduces the • Incidence of BPD • Incidence of death prior to 36 weeks postmenstrual age • Incidence of major complications of prematurity • Time to full feeds • Use of diuretics • Use of postnatal corticosteroids • Extent of respiratory support in the NICU Restricted compared to liberal fluid intake does not result in • Differences in growth • Differences in daily caloric intake • Differences in rates of dehydration • Differences in rates of fluid overload

	• Differences in postmenstrual age at discharge home • Differences in the rate of tube feeding at discharge home
Primary effectiveness outcome	The primary outcome is the proportion of infants with BPD measured at 36 weeks postmenstrual age or prior death. Outcomes are collected on patient-level, aggregated per centre and per 6-month period.

Secondary outcomes	Peri/-intraventricular brain haemorrhage will be documented as per SwissNeoNet standard and be included as a baseline variable. Despite being a common complication of prematurity, it will not be treated as a secondary outcome because it occurs prior to eligibility for this trial.
	
	Secondary outcomes include
	
	• Components of the primary composite outcome
	  ○ Bronchopulmonary dysplasia at 36 weeks postmenstrual age
	  ○ Death prior to 36 weeks postmenstrual age
	• Major complications of prematurity including
	  ○ Necrotising enterocolitis ≥ Bell's stage 2
	  ○ Retinopathy of prematurity requiring treatment
	  ○ Patent ductus arteriosus requiring treatment
	  ○ Abnormal brain ultrasound (composite of leukomalacia, ventricular dilatation, and porencephalic cysts)
	  ○ Late onset sepsis
	• Days to reach full feeds
	• Treatment with diuretics (days on diuretics)
	• Systemic postnatal corticosteroids for prevention or treatment of bronchopulmonary dysplasia
	• Duration of mechanical ventilation
	• Duration of non-invasive respiratory support
	• Duration of total positive pressure support
	• Duration of supplemental oxygen support
	• Supplemental home oxygen (suggested by PPI representatives)
	• Home ventilation (suggested by PPI representatives)
	• Growth (difference in weight, length, and head circumference z-score at 36 weeks postmenstrual age and at birth, respectively)
	• Daily caloric intake from day 8 of life to 36 weeks postmenstrual age
	• Dehydration (sodium level ≥ 150 mmol/L plus clinical signs of dehydration)
	• Fluid overload (sodium level ≤ 130 mmol/L plus clinical signs of fluid overload)
	• Postmenstrual age at discharge home
	• Tube feeding at discharge home (suggested by PPI representatives)

Exploratory outcomes	Exploratory outcomes will be assessed 6-12 and 18-24 months post-term to rule out unexpected late effects. We do not expect significant differences in these outcomes related to fluid intake in the NICU. Exploratory outcomes 6-12 months post-term include • Growth (weight, length, and head circumference z-score) • Respiratory outcome (BILD study questionnaire) • Visits to the emergency department from discharge to 6-12 months for any reason (suggested by PPI representatives)

	Exploratory outcomes 18-24 months post-term include • Growth (weight, length, and head circumference z-score) • Respiratory outcome (BILD study questionnaire) • Visits to the emergency department from 6-12 months to 18-24 months for any reason (suggested by PPI representatives) • Neurodevelopmental outcome (PARCA-R questionnaire)
Randomisation	NICUs are the unit of randomisation. Each of the 9 NICUs will be randomised to a sequence of 5 periods of 6 months, resulting in a recruitment period of 30 months. NICUs will cross over between 6-month-periods of restricted (135 mL/kg/d) or liberal fluid intake (165 mL/kg/d) for all infants born at < 30 weeks GA.
Number of infants expected during trial period (sample size estimate)	750 infants will be recruited to measure the primary outcome in 700 infants based on the following assumptions: Intra-cluster correlation coefficient 0.02, coefficient of cluster size variation 0.5, control prevalence of primary outcome 27%, reduced to 18% by fluid restriction, power 80%, alpha=0.05 (two-sided). The loss of n=50 participants over 30 months prior to primary outcome measurement is expected due to rare difficulties in reliably obtaining primary outcome data in infants who are transferred to stepdown nurseries before 36 weeks postmenstrual age. The trial management team and local investigators at NICUs will offer strong support in ascertaining alive/BPD status (primary outcome) in those infants who are transferred.
Washin/washout	Infants will remain on their initially allocated fluid regimen until reaching 36 weeks postmenstrual age, even if the cluster crosses over. Therefore, no washin/-out phase at cluster level is required.
Study duration	Total study duration: 60 months (1 January 2025 – 31 December 2029) Total duration of recruitment: 30 months (1 July 2025 – 31 December 2027)
Follow-up	Total duration of follow-up of each participant: 18-24 months beyond the expected date of delivery
Study site inclusion criteria	• Certified Swiss Level 3 NICU • Adequate resources and expertise and approvals from relevant Research Ethics Committees, as appropriate.
Study site exclusion criteria	• Unit-level fluid protocols incompatible with the strategy of comparing restricted vs. liberal fluid intake over 6-month-periods.
Eligible infants	Preterm infants born with a GA < 30 weeks, from day 8 of life.
Motivated deviations from fluid strategy	Infants may not be offered fluid restriction or liberal fluid intake in case of motivated deviations.
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