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# INnovative Steroid Treatment to reduce Asthma development in children after first-time Rhinovirus-induced wheezing (INSTAR): protocol for a randomised placebo-controlled trial

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## ABSTRACT

**Introduction** Asthma is a leading cause of morbidity and healthcare use among children. Risk factors of childhood asthma include atopic predisposition and severe wheezing episodes caused by rhinovirus infection in early life. In children with first-time rhinovirus-induced wheezing, we aim to study the response of a short corticosteroid treatment to prevent recurrent wheezing and asthma.

**Method and analysis** This is a double-blind, randomised, placebo-controlled, phase IV, international multicentre trial involving eight sites in Norway, Sweden and Finland. Two hundred and eighty 3–23 months old steroid-naïve children are randomised 1:1 to receive oral dexamethasone (0.3 mg/kg/day) versus placebo in 3 days for their first wheezing episode and rhinovirus infection. Rhinovirus is diagnosed with multiplex PCR. The two co-primary outcomes are time to next physician-confirmed wheezing episode, and time to asthma, within 24 months from inclusion. Asthma is defined as fulfilment of the 2007 National Asthma Education and Prevention Program—criteria for initiating asthma controller medication in children aged 0–4 years. Primary interaction analyses are age, gender, atopic predisposition, risk genotypes and viral co-detection. The optimal cut-off on the rhinovirus genome load used to define a true rhinovirus infection will be assessed by exploring interactions between rhinovirus genomic loads and study drug on the co-primary outcomes. Secondary outcomes are number of wheezing episodes, duration and severity of each wheezing episode, bronchial hyperreactivity, quality of life and safety (height/weight development) at 24 months from inclusion.

**Ethics and dissemination** Rhinovirus positive children with acute wheezing fulfilling inclusion and exclusion criteria are enrolled after informed consent from both caregivers. This trial has received ethical approval from all sites. Results will be submitted to Competent Authorities and disseminated via peer-reviewed publications and conferences within paediatrics and other relevant fields. If proven effective, findings may be implemented directly into paediatric clinical guidelines.

**Trial registration number** NCT03889743.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This trial is an adequately powered randomised clinical trial to study whether corticosteroid treatment during the first wheezing episode in rhinovirus infected children may prevent recurrent wheezing and asthma development.
⇒ The multicentred design all year round across three Nordic countries increases the generalisability of the findings.
⇒ The parent-child perspective is included through repeated quality of life assessments during follow-up.
⇒ Since a true rhinovirus infection is not clearly defined, in this trial, we will assess the impact of rhinovirus genomic loads.
⇒ A limitation of this trial is the lack of sensitive diagnostic tools for detecting a true rhinovirus infection, as available PCR tests have limited specificity as non-live virus particles may sometimes persist after a respiratory infection.

## INTRODUCTION

Asthma is the most common chronic disease of childhood and a leading cause of emergency department visits and hospitalisations among children.[1] Main conventional risk factors of childhood asthma include atopic predisposition (atopic dermatitis, parental asthma and/or aeroallergen sensitisation) and severe early wheezing episodes.[2–5] Other risk factors are male gender, number of early respiratory tract infections,[4 5] exposure to air

pollutants[6] and secondhand smoking.[7] Genetic predisposition may be an important host factor in asthma development.[8–10] The main stream of asthma treatment is to control airway inflammation by regular inhaled, or in acute phases by systemic, corticosteroids.

Viral infections lead to repeated cycles of inflammation that over time disturb several mechanisms involved in the maintenance of immunological homeostasis in the airways.[11] Viral aetiology of bronchiolitis has gained interest as a tool for early identification of high asthma-risk children, with respiratory syncytial virus (RSV) and rhinovirus being the main agents of investigation. The clinical manifestations of RSV and rhinovirus infections are different, as is the subsequent asthma risk associated with early life infection with either agent. RSV-induced bronchiolitis is characterised by young age and mechanical obstruction of the airways due to mucus and cell debris.[12] Along with parental smoking and diminished lung function, it has been modestly associated (10%–30%) with recurrent wheezing and subsequent non-atopic asthma.[12 13] Rhinovirus-induced wheezing is associated with older age,[12] atopic predisposition and increased risk of atopic asthma (30%–80%).[14–16] Rhinovirus dominates as an aetiologic agent from the second year of life[16 17] and is the most common trigger of recurrent wheezing in older children.[16] During the past two decades, rhinovirus-induced early wheezing has been recognised as a greater risk factor for recurrent wheezing and atopic asthma than RSV.[14–16] Atopic children are more susceptible to rhinovirus-induced wheezing, and aeroallergen sensitisation markedly increases rhinovirus-wheeze associated asthma risk.[18 19] Genetically, the rhinovirus-associated asthma risk may be related to a missense variant at the cadherin-related family member 3 (CDHR3) gene and variants at the 17q21 locus.[8 9] CDHR3 serves as a receptor for rhinovirus type c and is associated with rhinovirus type c illnesses,[9] while variants at the 17q21 locus have been associated with rhinovirus wheezing illnesses and number of rhinovirus wheezing illnesses in the first 3 years of life.[8]

Besides a short-term beneficial effect through vasoconstriction and improvement in β-agonist responsiveness, systemic corticosteroids have a long-term anti-inflammatory effect. Jartti and colleagues[18–23] investigated in two clinical trials whether response to systemic corticosteroids is rhinovirus specific. The first exploratory study (Vinku) randomised wheezing children of all ages to a 3-day course of prednisolone (2 mg/kg/day) or placebo, and results were analysed post hoc according to patient characteristics and viral aetiology in children aged <3 years and with their first or second wheezing episode.[20] Prednisolone was not associated with an overall efficacy, but the treatment was associated with less recurrent wheezing and asthma in rhinovirus (n=34) (adjusted HR 0.32, 95% CI 0.12 to 0.90) and/or eczema (n=36) (adjusted HR 0.27; 0.08–0.87) groups at 7-year follow-up.[18] These findings led to a new prospective randomised controlled trial (RCT), Vinku2, in which rhinovirus-positive first-time wheezing children aged 3–23 months (n=74) received either prednisolone with similar dosage or placebo. Overall, prednisolone was not effective, but the main interaction analysis included rhinovirus genome load. The children with rhinovirus genome load of >7000 copies/mL and receiving prednisolone had less recurrences and less need for regular asthma controller medication at a 4-year follow-up (HR 0.38, 95% CI 0.14 to 1.01).[22] Interestingly, regular asthma controller medication was started within 14 months in all children with high rhinovirus genome load in the placebo group.[22] Both Vinku trials showed 30% less asthma during the 4–7-year follow-up in the active treatment groups. The weaknesses of these trials were small sample sizes, post hoc analysis in Vinku and secondary outcome analysis in Vinku2; nevertheless, they suggest a long-term beneficial effect of corticosteroids in young children with rhinovirus-induced first wheezing episode. Since corticosteroids do not affect viral replication, a likely explanation is that early airway inflammation (typically type 2 polarised) increases susceptibility to rhinovirus, and corticosteroids effectively downregulate these early inflammatory events in these asthma-prone children.

The current paper describes the protocol of the *INnovative Steroid Treatment to reduce Asthma development in children after first-time Rhinovirus-induced wheezing* study (INSTAR), an on-going multicentre randomised placebo-controlled trial (RCT) that aims to prevent asthma development by intervening with a 3-day systemic corticosteroid course at the first wheezing episode in >3 to <24-month-old children with rhinovirus infection. If INSTAR confirms the highly relevant findings of the Vinku trials, this could directly influence clinical guidelines and be a breakthrough in preventative paediatric asthma treatment.

### Objectives

The primary objective is to determine the efficacy of systemic corticosteroids in preventing recurrent wheezing and asthma in first-time severely wheezing children with rhinovirus infection, stratified by rhinovirus genome load. The secondary objectives are to determine the number of wheezing episodes, severity and duration of each acute wheezing episode, degree of bronchial hyperreactivity and quality of life (QoL) within 24 months follow-up.

## METHODS AND ANALYSIS

### Trial design

INSTAR is a pharmaceutical phase IV, multicentre, placebo-controlled RCT, conducted in Norway, Finland and Sweden. The RCT has two treatment groups (1:1): corticosteroid treatment and placebo (figure 1). The first patient was included in May 2019, and completion of the last patient is expected in May 2028.

### Study setting

INSTAR is conducted at eight paediatric departments in Norway, Finland and Sweden and is active all year round, with expected recruitment peaks in

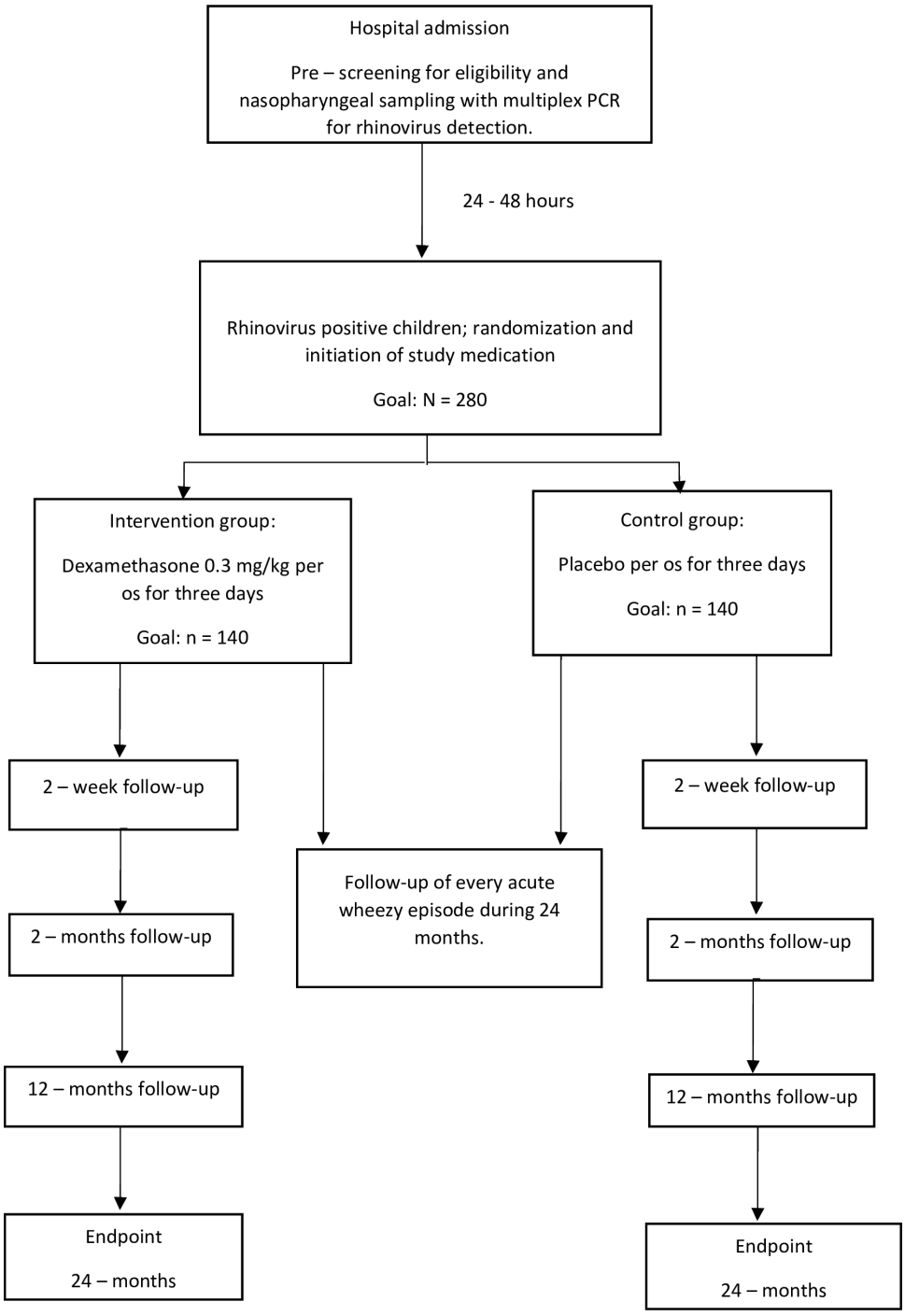


**Figure 1** Flowchart of study participants in the randomised placebo-controlled trial INnovative Steroid Treatment to reduce Asthma development in children after first-time Rhinovirus-induced wheezing (INSTAR).

September–December and March–May. St. Olavs hospital, Trondheim University Hospital (St. Olavs) in Trondheim, Norway is the sponsor and the coordinating site. In Norway, six university hospitals in all four healthcare regions participate: St. Olavs, Akershus University Hospital, Oslo University Hospital, Stavanger University Hospital, Haukeland University Hospital in Bergen and University Hospital of Northern Norway. In Finland and Sweden, University Hospital of Turku (TYKS) and Karolinska University Hospital, Stockholm (KUH), participate. All participating hospitals have paediatric departments and are run by public healthcare trusts.

Identification and enrolment of participants take place at paediatric emergency wards (ERs) or in-patient wards. Most children in Norwegian ERs are referred to hospital by a general practitioner. In Sweden and Finland, patients may also seek hospital without a referral. Follow-up visits are organised at outpatient clinics or paediatric research units at the hospitals.

Table 1 Eligibility criteria

| Inclusion criteria | Exclusion criteria |
|---|---|
| First acute severe wheezing episode,* with one or more of: | Previous episode with wheezing, defined as a history of acute breathing difficulty with wheezing in need of treatment at a general practitioner or hospital, or parental information about similar breathing difficulties. |
| Fever | Gestational age <37 weeks. |
| Oxygen saturation ≤92% | Chronic illness other than atopy. |
| Inter- or subcostal chest retractions | Previous systemic or inhaled corticosteroid treatment. |
| Prolonged expiration on auscultation | COVID-19 related disease. |
| Expiratory rhonchi on auscultation | Participation in another trial. |
| Evidence of rhinovirus infection by PCR test in nasopharyngeal secretions | Varicella infection or contact during the last 2–3 weeks. |
| Signed, informed parental consent according to ICH-GCP† and expected parental cooperation for treatment and follow-up | Need for intensive care unit treatment during the present infection, except for respiratory support with high flow nasal cannula ventilation |
| | Any reason why, in the opinion of the investigator, the patient should not participate, for example, social or psychiatric conditions in the family that will hamper compliance or make participation a burden to the family |

*'First acute wheezing episode' is within the study setting defined as 'first-time acute breathing difficulty with wheezing ever, appearing less than 7 days from onset of respiratory symptoms, in a child referred to or seeking hospital'.
†International Council for Harmonisation Good Clinical Practice (ICH-GCP) Guidelines.

## Subjects

The study population is 3–23 months old, steroid naive children referred to or seeking hospital for their first acute, severe wheezing episode. 'First acute wheezing episode' is defined as 'first-time acute breathing difficulty with wheezing ever, appearing less than 7 days from onset of respiratory symptoms, in a child referred to or seeking hospital'. To qualify for study treatment, the child must have evidence of rhinovirus infection by PCR test in nasopharyngeal secretions (NPS). Viral co-infection is allowed. The severe wheezing is ensured by the inclusion criteria listed in table 1. Signed informed consent and expected cooperation of the parents for treatment and follow-up must be obtained and documented according to International Council for Harmonisation Good Clinical Practice (ICH-GCP) guidelines. Children disqualify from participating if they meet any of the exclusion criteria (table 1).

## Study intervention

The Investigational Medicinal Product (IMP) in INSTAR is Dexametason Abcur 1.0 mg tablets (pharmacotherapeutic group glucocorticoids, ATC-code H02AB02) and placebo tablets, both produced at Cyndea Pharma S.L., Spain, and shipped to the hospital pharmacies in Trondheim, Norway, and Turku, Finland. The hospital pharmacies re-pack, label and certify the IMP, and release it to the sites in appropriate batches. The IMP is stored in clinical medicine rooms until dispensing to study participants. Dexamethasone was chosen as IMP as it has a longer biological half-life than prednisolone, is proven to be equivalent in treatment of paediatric asthma exacerbations and is less likely to cause emesis.[24]

The IMP dosage equals dexamethasone 0.3 mg/kg/day (table 2), given once per day over three consecutive days, or the equivalent number of placebo tablets. IMP intake within 18–30-hour intervals is defined as protocol compliant. Study treatment starts when the child's viral report is available and parental consent is obtained, which normally is within 24–48 hours from hospital admission.

The IMP is administered and documented according to hospital routines in in-patients and administered by parents in out-patients. Source data of parental IMP administration is documented in a 2-week symptom diary and further inquired in a scheduled telephone interview 2–4 days after inclusion and at the first scheduled clinic visit in 2 weeks. Return of left-over IMP is not required. Drug accountability is kept of receipt, dispensing to patients and destruction of unused/expired IMP.

## Randomisation and masking

This trial uses computerised block randomisation stratified by centre, with varying block sizes and a 1:1 allocation ratio between dexamethasone and placebo. Site-specific randomisation numbers are obtained from a master randomisation list which is generated by the Research

Table 2 Daily dosage of IMP according to body weight

| Body weight* | Dexamethasone Abcur 1.0 mg | Placebo |
|---|---|---|
| 5–7.99 kg | 2.0 mg x 1 (2 tablets) | 2 tablets |
| 8–10.99 kg | 3.0 mg x 1 (3 tablets) | 3 tablets |
| 11–13.99 kg | 4.0 mg x 1 (4 tablets) | 4 tablets |
| 14–16.99 kg | 5.0 mg x 1 (5 tablets) | 5 tablets |
| 17–20 kg | 6.0 mg x 1 (6 tablets) | 6 tablets |

*Kilograms.
IMP, Investigational Medicinal Product.

Department, Norwegian University of Science and Technology (NTNU) and St. Olavs, and labelled on each medicine glass. Only hospital pharmacists have access to the allocation codes. The trial is triple blinded.

## Concomitant care

Given the heterogeneity of childhood wheezing illnesses,[12 25] the study participants are treated based on their clinical presentation in accordance with paediatric guidelines[25–28] used in Norway, Finland and Sweden. Care, including inhaled salbutamol, is ordinated at the discretion of the attending physician. In case of deterioration of the illness, the investigation will be terminated, the randomisation code may be opened, and the participant treated with routine care.

## Outcomes

The co-primary outcomes are time to the next physician-confirmed wheezing episode within 24 months from inclusion, and time to fulfilling criteria for asthma within 24 months from inclusion. A new wheezing episode is defined as the appearance of acute breathing difficulties with expiratory wheezing, as evaluated by clinical examination in the ERs, at paediatric outpatient clinics or at general practitioners. A new wheezing episode may also be evaluated through digital consultation with a paediatrician. Asthma diagnosis is defined as fulfilment of the 2007 National Asthma Education and Prevention Program (NAEPP) – criteria[27] for initiating regular (≥4 weeks) asthma controller medication in children aged 0–4 years. Time is measured in number of days.

Interaction variables to the co-primary outcomes, considered to be explorative, are age,[18 21] gender,[29] atopic predisposition, as indicated by presence of atopic eczema,[18 19 21] blood eosinophilia[20] and allergic sensitisation,[19 30] risk genotypes including 17q21 locus[8] and CDHR3 polymorphisms,[9 31] and viral co-detections, including RSV.[4 32] The optimal cut-off on the rhinovirus genomic load indicating a true rhinovirus infection will be assessed by exploring interactions between rhinovirus genomic loads and treatment on the primary outcome variables.

The secondary outcomes are measured within 24 months from inclusion and are number of wheezing episodes, duration of each wheezing episode, measured in number of days of symptom duration for each respiratory symptom and severity of each new episode. Episode severity is determined by length of hospital stay (LOS), use of supportive treatments and oral corticosteroids. Other secondary outcomes are bronchial hyperreactivity, QoL and safety (height/weight development). Bronchial hyperreactivity is measured overnight with impedance pneumography (IP)[33 34] (TYKS only). QoL is measured with the generic Infant/Toddler Quality of Life Questionnaire-97,[35] HealthActCHQ Inc.

## Study procedures

### Recruitment and enrolment

All children are evaluated according to hospital practice at admission. Consent to participate in the trial is obtained by study personnel, whereas the initial screening for eligibility may be performed by on-duty physicians. In accordance with ICH-GCP guidelines, trial training is given to on-duty physicians who are delegated to screen patients. Usually, INSTAR is introduced to parents of eligible children as a part of the clinical routine. A short INSTAR brochure in lay language is handed out along with a brief oral presentation of the study, and a nasopharyngeal swab specimen (NPS) is obtained for multiplex PCR. In Sweden, parental consents are obtained before the NPS, whereas in Finland NPS belongs to hospital routine. In Norway, oral consent is needed if the sample is obtained for trial screening only. In Norway and Finland, in-patients who were not identified at admission could be screened at the ward (online supplemental table 1). When the viral report is available, parental consents are obtained from rhinovirus positive children and study procedures (online supplemental table 1) commence.

### Follow-up

Follow-up visits are scheduled 2 weeks, 2 months, 12 months and 24 months after inclusion and telephone contacts after 2–4 days, 6 months and 18 months (online supplemental table 1). The scheduled visits comprise physical examinations, parental questionnaires, biological samplings, QoL assessments[35] and IP measurements at home (TYKS only).[33 34] The parental questionnaires at 2 weeks and 2 months summarise symptoms duration and number of days with salbutamol, with 2-week and 2-month symptom diaries as source data documentation. A symptom diary of acute respiratory events is filled from 2 to 24 months. The 12 and 24 month parental questionnaires are based on the 5-item Test for Respiratory and Asthma Control in Kids.[36] New wheezing episodes are inquired at every scheduled contact. In cases of parentally reported doctor appointments for wheeze or other respiratory events, medical records are obtained and reviewed by the study physician or PI. If acute or persistent (≥4 weeks) wheezing is documented, the episode is recorded as a new wheezing episode and/or fulfilment of the asthma diagnostic criteria (NAEPP).

Parents are encouraged to contact the paediatric departments in cases of new wheezing episodes or persistent respiratory symptoms during follow-up. To ensure admittance to the ER without referral, open return to hospital is documented in the child's medical records. LOS, clinical signs and symptoms, treatments and duration of wheeze and other respiratory symptoms are recorded prospectively for each wheezing episode confirmed at the sites. Weekly phone interviews are conducted until 3 weeks after the clinical evaluation to record symptom duration (online supplemental table 1). Fulfilment of the asthma diagnostic criteria is evaluated at each visit. ICS prescriptions are confirmed at 24 months by national registries

of drug purchases (online supplemental table 1). The regular scheduled contacts and open return to hospital facilitate precise recordings of outcome data and prevent parental recall bias.

### Specimen sampling and storage

At the Norwegian sites and TYKS, specimens are processed and stored locally and transferred to Biobank1, Trondheim, Norway for long-term storage (online supplemental table 1). Swedish specimens are processed and long-term stored at BioClinicium, KUH.

#### *Microbiological material*

A NPS in 3 mL Copan Italia S.p.A. universal transport medium for viruses is collected at admission for local PCR and later rhinovirus load quantification and immunological research, and at every scheduled visit for later immunological research. Mucosal lining fluids are collected with Nasosorption™,[37] and faecal samples with OMNIgeneGUT for microbiome (OM-200). DNA Genotec Inc., Ottawa, ON, Canada

#### *Blood and biochemistry*

Blood samples are collected by venipuncture. Whole blood is collected for local analysis of eosinophils, peripheral blood mononuclear cells isolation, and later candidate gene and genome wide association studies. Serum is collected for local analysis of allergy panels and later research. In all, ~10 mL blood is collected at each visit. A priority list is made in cases of low body weight.

## Sample size calculations

The target population of INSTAR is children with rhinovirus-induced wheezing. Multiplex PCR panels often detect more than one virus. However, available PCR tests have limited specificity as non-live virus particles may sometimes persist after a respiratory infection. We thus have a reason to suspect that patients who test positive for rhinovirus and have a low viral load may not have a true rhinovirus infection. We do not expect any clinically relevant treatment effect for low viral loads, and 7000 copies/mL has earlier been suggested as a limit for categorising into high (actual rhinovirus infection during the current episode) and low viral load (no true infection).[22] We therefore used a pragmatic approach assuming a 40%/60% distribution of high and low viral loads in rhinovirus positive children.[22] Sample size was calculated for a Cox regression analysis for the high load subgroup, and for a similar analysis based on the whole sample (whatever load). Using Cox regression, we estimate the HR between corticosteroid and control groups for the two primary outcome variables (time to recurrence of a new wheezing episode and time to fulfilling criteria for asthma). The follow-up period is 24 months, and a 15% dropout rate is accounted for. The sample size calculations depend on the assumed hazard rates and event occurrence at 24 months in the dexamethasone and placebo groups. In previous studies, hazard rates (HRs) of 0.2 for time to recurrence[23] and 0.38 for time to asthma diagnosis[22] were estimated between prednisolone and placebo in the high load group. Calculations are made for assumed hazard rates of 0.5, a slightly smaller effect size than in[22] and.[23] Calculations are performed using the command *power cox* in Stata.

### Outcome: time to recurrence within 24 months

#### High rhinovirus load

It has been estimated that 100% of children receiving placebo will have a new wheezing episode within 24 months.[23] An event probability of 95% is assumed in the calculations. A reduction of event occurrence at 24 months of at least 20 percentage points to 75% in the corticosteroid group is considered clinically relevant. Using 80% power and 5% significance level, 77 children will be needed in total. Considering dropout, a total of 91 children is needed.

#### High and low rhinovirus load

It has been estimated that approximately 85% of children (whatever load) receiving placebo will have a new wheezing episode within 12 months[23] and is assumed as event probability at 24 months as well. A 20 percentage points reduction is considered clinically relevant. Using 80% power and 5% significance level, 88 children will be needed in total. Considering dropout, a total of 104 children are needed.

### Outcome: time to asthma within 24 months

#### High rhinovirus load

It is estimated that 100% of children receiving placebo will fulfil criteria for asthma within 24 months.[22] An event probability of 95% is assumed. A reduction to 75% for children in the corticosteroid group is considered clinically relevant. Using 80% power and 5% significance level, 77 patients will be needed in total. Considering dropout, a total of 91 children are needed.

#### High and low rhinovirus load

It has been estimated that approximately 70% of children (whatever load) receiving placebo will fulfil criteria for asthma within 24 months.[22] A reduction to 50% is considered clinically relevant. Using 80% power and 5% significance level, 109 patients will be needed in total. Considering dropout, a total of 129 children are needed.

To ensure a sufficient sample of children with a true rhinovirus-induced infection (n=91), the trial must enrol at least 91/0.4=228 rhinovirus positive children. Following a pragmatic increase due to uncertainty in the assumed input values, we plan to include 280 children.

## Statistical analyses

The intention to treat (ITT) population, per-protocol population and safety population will be considered for statistical analysis. A list of withdrawn participants, preferably with reason for withdrawal, will be made. The final statistical analysis plan (SAP) will be finalised, signed and dated before database lock. Treatment allocation will not be revealed until the primary outcomes are analysed.

If missing data is regarded as having a significant effect on the conclusions of the trial, sensitivity analysis with different methods for handling missing data will be included.

### Primary outcome variables

The primary outcome variables will be analysed by Cox proportional hazard regression analysis with treatment allocation and study site as covariates. The analysis will be performed on the ITT population. The analyses will be performed for the whole sample and for the high and low load subgroup, even though no treatment effect is expected for the latter. In addition, the modifying effects of a set of pre-specified covariates (see Outcomes) will be investigated by including interaction effects between treatment group and these variables in the Cox regression models. Optimum rhinovirus cut-offs will be investigated by testing for different values and selecting the approximate threshold that yields the best model fit.

The adjusted HRs between treatment and placebo for the primary outcomes will be presented with 95% CI, calculated from the Cox regression. Withdrawn and lost to follow-up patients will be censored at the time of dropping out. P values <0.05 will be considered statistically significant. No formal p value adjustment for multiple primary outcomes is made, but the results for both primary outcomes will be interpreted jointly, with due consideration to the issue of multiple testing.

### Secondary outcome variables

The secondary outcome variables will be analysed on the ITT and per-protocol populations. Continuous variables will be subject to linear mixed models or appropriate non-parametric alternatives. Binary response variables and count data will be analysed by generalised linear mixed models. By using mixed models, within-subject dependencies due to repeated measurements will be taken into account. Results will be presented as estimated effects with 95% CI and p values. No formal adjustment for multiple testing is planned, but the issue of multiple testing will be kept in mind when interpreting the results.

### Safety analysis

Safety analyses will be performed by an independent Data Safety and Monitoring Committee (DSMC) after completion of 12 months follow-up for 100 patients and presented as summary tables by treatment group. The frequencies of adverse events (AE and SAE) will be compared with $\chi 2$ tests, and height/weight measurements between groups will be analysed with T-tests. The DSMC will follow recruitment and safety yearly on indication.

### Exploratory analysis

Exploratory immunologic, genetic and microbiological analyses in relation to response to the corticosteroid intervention, patient characteristics, and IP data, and prognoses will be further specified in the SAP.

### Patient and public involvement

A user representative from the Norwegian Asthma and Allergy Association[38] is appointed through St. Olav's board for user involvement. Given the caregiver burden of asthmatic children[39] and the reduction in QoL that is observed after bronchiolitis,[40 41] our choice of outcome measures is meaningful from a parent-patient perspective.

## ETHICS AND DISSEMINATION

### Ethical and safety considerations

This trial is approved by the Regional Committee for Medical and Health Research Mid-Norway (2018/1495), the Ethics committee of hospital district of South-West Finland (61/1800/2015) and the Swedish Ethical Review Authority (2019–0543). The procedures followed through all phases of the trial are based on Standard Operating Procedures on the conducting of clinical research from the Norwegian Clinical Research Infrastructure Network.[42] Informed, written consent is voluntarily given, with mandatory signature from one parent at inclusion and consent by mail/SMS from the other caregiver, to be confirmed with a written signature within 2 weeks (online supplemental material). The families of participating children are not compensated financially, but each child receives gifts worth in total 100 €. Parents are not informed about the gifts beforehand.

Dexamethasone is registered for use in children with asthma. Expected side effects from corticosteroid treatment are vomiting, rashes, lethargy, irritability, anxiety and insomnia; however, minimal side effects are expected from the prescribed doses.[43] Height and weight are recorded at every scheduled visit, and AEs are registered, evaluated and followed up until resolution 1 month from the last dose of IMP for each child. The hospital pharmacies are available 24 hours for emergency un-blinding. No more than 1% of the children's blood volume is sampled at each visit, which poses minimal risk.[44]

Conducting research on young children requires ethical considerations. Nasopharyngeal sampling[45] and venipuncture[46] are unpleasant, and both procedures are done repeatedly in INSTAR. Encouragingly, Padding *et al* found that 5 and 6 years olds experienced little emotional burden during invasive procedures in asthma research, including nasal swabs and venipuncture.[46] Few studies have examined preschool children's experiences in undergoing research procedures, but the findings of Padding *et al* are supported by a study on older children from the UK. Eight to fifteen-year-old childhood cancer patients and parents participating in optional non-therapeutic clinical studies reported participation as an overwhelmingly positive experience, and ~90% of patients and parents would participate in future studies.[47] Despite possible discomforts related to the research procedures, better outcomes have been demonstrated for children participating in clinical trials compared with children not participating, even when allocated to the control group.[48]

## Data management and monitoring

The Research Department, NTNU/St. Olav oversees data management and monitoring. The electronic CRF *WebCRF*[49] is used for online data entry and management. Data are entered pseudonymised with site specific subject identification numbers. Patient files and subject identification logs are kept with restricted access at each site, accessible to study personnel only. The monitoring plan in INSTAR is risk-based, with full source data verification of primary outcome variables and specified interacting factors and clinical review for data related to secondary endpoints. Monitors and competent authorities are allowed to access patient files and medical records for source data verification.

## Recruitment status

By March 2025, we had recruited half of the estimated required number of patients. The COVID-19 pandemic with periodical national lockdowns in Finland, Sweden and Norway affected our recruitment rate, with re-allocation of study personnel, rhinovirus being taken out of routine panels at some sites and the epidemiology of airway viruses changing, with less admittances of eligible children at all participating sites during 2020 and 2021.[50–52]

## Dissemination

The results of INSTAR will be submitted for publication in the Clinical Trials Information System and submitted to peer-reviewed medical journals in the scope of research papers. The authors will be listed according to the Vancouver convention (1988). Additionally, results will be presented at scientific conferences within relevant fields.

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