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A randomised placebo-controlled multi-centre effectiveness trial of adjunct betamethasone therapy in hospitalised children with community acquired pneumonia – trial protocol for the KIDS-STEP trial

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ABSTRACT

Introduction: Community-acquired pneumonia (CAP) causes around 10 hospitalisations per 1000 child-years, each associated with an average 13 non-routine days experienced and more than 4 parent workdays lost. In adults, steroid treatment shortens time to clinical stabilisation without an increase in complications in patients with CAP. However, despite promising data from observational studies there is a lack of high-quality evidence for the use of steroids.

Methods and analysis: The KIDS-STEP trial is a multicentre, randomised, double-blind, placebo-controlled superiority trial of betamethasone treatment on outcome of hospitalised children with CAP. Children are enrolled in paediatric emergency departments of hospitals across Switzerland and randomised to adjunct oral betamethasone for 2 days or matching placebo in addition to standard of care treatment. The co-primary outcomes are the proportion of children clinically stable 48 hours after randomisation and the proportion of children with CAP-related readmission within 28 days after randomisation. Secondary outcomes include length of hospital stay, time away from routine childcare and healthcare utilisation and total antibiotic prescriptions within 28 days from randomisation.

Each of the co-primary outcomes will be analysed separately. We will test clinical stability rates using a proportion test; to test non-inferiority in readmission rates, we will construct 1-α % confidence interval of the estimated difference and test if it contains the pre-defined margin of 7%. Success is conditional on both tests. A simulation-based sample size estimation determined that recruiting 700 patients will ensure a power of 80% for the study.

Ethics and dissemination: The trial protocol and materials were approved by ethics committees in Switzerland (Ethikkommission Nordwest- und Zentralschweiz) and the regulatory authority Swissmedic. Participants and/or caregivers provide informed consent prior to study procedures commencing. The trial results will be published in peer-reviewed journals and at national and international conferences. Key messages will also be disseminated via press and social media where appropriate.

Trial registration number: NCT03474991, SNCTP000002864

Strengths and limitations of this study:

- This well-powered multi-centre trial will provide high quality evidence on efficacy of adjunct steroid treatment for uncomplicated CAP in children
- As clinically defined CAP contains mixed severities and aetiologies, overall results may miss divergent effects in specific subpopulations
- Despite exclusion of children with alternative diagnoses, a clinical diagnosis may have limited specifity for CAP
- The pragmatic approach to eligibility employed by the KIDS-STEP trial is aligned with clinical practice and so will facilitate rapid knowledge translation.
- The generalisability of the KIDS-STEP trial findings will be maximised by the wide age range and the diverse aetiology of CAP in the enrolled population

INTRODUCTION

The incidence of community-acquired pneumonia (CAP) in young children remains high (30-40/1000 child-years) even in high-income settings with routine pneumococcal vaccination, and is associated with a high rate of hospitalisation (around 10/1000 child-years).[1] In low- and middle-income settings, pneumonia is the leading infectious cause of death in children less than 5 years of age.[2] In high-income settings, working mothers of children hospitalised with CAP have been reported to lose on average 4.2 workdays compared with 1.7 workdays for children with CAP managed in primary care.[3] In addition to this economic burden, there is a substantial impact on quality of life for the affected child and the family.[3] Children who are admitted with CAP experience on average 13 non-routine days as judged by their parents or caregivers when assessed with a standardised quality of life questionnaire. Periods of decreased appetite (8.5 days), disordered sleep (4.5 days) and absence from routine out-of-home childcare (7.5 days) were slightly shorter.[3] Any intervention that ensures rapid clinical stabilisation allowing for early hospital discharge without negative impacts on the overall recovery in children hospitalised with CAP would therefore carry substantial socioeconomic benefits.

Adjunct systemic corticosteroids shorten the time until clinical stability is reached in adult patients.[4] Comparable data for paediatric patients applicable to an unselected group of children with moderate-severe CAP are not available. The most recent Cochrane meta-analysis found evidence for a benefit from steroid treatment, but for children this was based on a small number of very heterogenous and mostly unblinded trials aiming to investigate the efficacy of steroids in pneumonia with detection of specific pathogens, for example *Mycoplasma pneumonia*e or respiratory syncytial virus (RSV).[5]

Infection-related unwanted effects of adjunct steroids are potentially relevant in the context of childhood CAP. A higher proportion of children hospitalised with CAP reaching early clinical stability would only be desirable if this would not to be offset by a higher rate of clinically relevant CAP recurrence. A rebound phenomenon after corticosteroid discontinuation has been postulated to explain a higher rate of infection recurrence (19% compared with 9% in placebo group) among adults.[6] Data from a recent individual patient data meta-analysis, however, indicate that an increased risk of CAP recurrence may be observed,[7] potentially associated with a longer duration of adjunct steroids in adults with CAP. To our knowledge, the question about the effect of adjunct steroid treatment in childhood CAP in relation to a postulated rebound

phenomenon measured clinically as CAP recurrence has not been formally addressed in a trial. CAP-specific readmission rates for children are low at around 5%.[8 , 9] In bronchiolitis, another acute lower respiratory tract infection for which oral corticosteroid treatment has been investigated, an increased risk of hospital revisits associated with steroid treatment could not be identified in a Cochrane meta-analysis.[10] WHO has identified studies on the effect of steroids in the novel coronavirus disease (COVID-19) as a priority during the current pandemic.[11] While there is no evidence suggesting a harmful effect of steroids on paediatric patients, studies in adults have identified a longer duration of viral shedding after steroid treatment as a potential adverse effect in other coronaviruses.[12]

The primary objective of the trial is to concurrently evaluate

- whether treatment of children hospitalised for CAP with oral betamethasone is superior to placebo in terms of the proportion of children reaching clinical stability (defined as ready for discharge or with normal vital signs) at 48 hours after hospitalisation;
- whether inpatient treatment of childhood CAP with oral betamethasone is non-inferior to placebo in terms of the proportion of children with CAP-related readmission to hospital up to 28 days after randomisation.

Secondary objectives include the evaluation of effects of oral betamethasone treatment (versus placebo) in children hospitalised for CAP on:

- duration of primary hospital stay;
- severity and duration of CAP symptoms;
- parental absence from work and/or child absence from routine out-of-home care or school;
- overall duration of antibiotic exposure and inpatient days during the follow-up period;
- intensive care unit admissions;
- mortality;
- rate and severity of solicited clinical adverse events

METHODS AND ANALYSIS

KIDS-STEP is a phase III strategic investigator-initiated, randomised, placebo-controlled, fully blinded multicentre superiority trial with two parallel groups. Eligible children aged 6 months to less than 14 years and hospitalised with CAP at participating sites are randomised 1:1 to receive either adjunct oral betamethasone 0.1-0.2 mg/kg per day for 2 days (Celestamine®, a liquid formulation; 0.5 mg betamethasone per mL) or to receive oral placebo (matched in aspect, taste and dose) for 2 days in addition to regular standard of care. Dosing is done by 5kg weight bands (table 1). Randomisation is stratified by site. Data on on-going symptoms and healthcare services utilisation is collected daily until discharge from hospital and during 3 telephone follow-up visits up to and including at 4 weeks. While in hospital, vital signs and temperature are assessed at least every 8 hours. A trial flow chart is presented in figure 1.

Table 1: Dosing table for dose selection of betamethasone and placebo solutions

Weight band	Weight range (kg)	mg/ dose	Millilitres per dose
0	≥5 – <7	1.0	2
1	≥7 – <10	1.5	3
2	≥10 – <15	2.0	4
3	≥15 – <20	2.5	5
4	≥20 – <25	3.0	6
5	≥25 – <30	3.5	7
6	≥30 – <35	4.0	8
7	≥35 – <40	4.5	9
8	≥40 – <45	5.0	10

Trial setting

KIDS-STEP recruits participants in paediatric emergency departments of secondary and tertiary hospitals across Switzerland where potentially eligible patients present and can be admitted for inpatient care. Participants are recruited throughout the year.

Trial population

Children from age 6 months weighing at least 5 kilograms and up to a body weight of 45 kilograms admitted to one of the participating sites with signs and symptoms of CAP are considered potentially eligible for participation. Eligibility criteria are listed in table 2.

Table 2: Eligibility criteria

<table>
<tr><th colspan="2">Inclusion criteria (all must be fulfilled)</th></tr>
<tr><td>At least 6 months of age and less than 14 years of age</td><td rowspan="6">A. Temperature >= 38°C measured by any method or history of fever in last 48 hours reported by parents
AND
B. at least two of the following signs and/or symptoms:
- Presence of cough (observed or reported in last 72 to 96 hours)
- Increased age-specific respiratory rate as defined by American Heart Association Accredited Pediatric Advance Life Support guidelines during assessment in the paediatric emergency department (first or second triage or clinical examination)
- Hypoxaemia (<92% arterial oxygen saturation) in room air as measured by pulse oximetry (SpO2) [13 , 14]
- Signs of laboured/difficult breathing, including nasal flaring, chest retractions, grunting, abdominal breathing and shortness of breath
- Clinical signs of lobar pneumonia including focal dullness to percussion, focal reduced breath sounds, crackles with asymmetry</td></tr>
<tr><td>Body weight between 5 kg and 45 kg</td></tr>
<tr><td>Admission to hospital (i.e. assignment of an inpatient case number or receipt of in-hospital treatment in a designated short stay unit)</td></tr>
<tr><td>Clinical diagnosis of CAP</td></tr>
<tr><td>Parent and/or child (as age-appropriate) willing to accept all possible randomised allocations and to be contacted for three telephone follow-up visits up to and including at 4 weeks after randomisation</td></tr>
<tr><td>Informed consent form for trial participation signed by participants and/or caregivers</td></tr>
<tr><th colspan="2">Exclusion criteria (excluded if any of the following are present)</th></tr>
<tr><td colspan="2">- Presence of local complications (empyema or pleural effusion with clinically identified need for drainage, pneumothorax, and pulmonary abscess).
- Chronic underlying disease associated with an increased risk of very severe CAP or CAP of unusual aetiology, such as sickle cell disease, primary or secondary immunodeficiency, chronic lung disease and cystic fibrosis.
- Bilateral wheezing without focal chest signs AND clinical indication for primary administration of steroids (most likely to represent respiratory tract infection affecting the medium airways, i.e. not pneumonia).
- Admission to hospital with a primary clinical diagnosis of bronchiolitis.
- Inability to tolerate oral medication.
- Documented allergy or any other known contraindication to any trial medication.
- Subacute or chronic conditions requiring higher betamethasone equivalent or known primary or secondary adrenal insufficiency.
- Known diabetes mellitus (type 1).
- Hospitalisation within the last two weeks preceding current admission with the possibility that pneumonia could be hospital-acquired or healthcare-associated.
- Completion of a course of systemic corticosteroids within 2 weeks from enrolment for courses of >5 days.
- Transfer for any reason to a non-participating hospital directly from the paediatric emergency department.
- Parents are unlikely to be able to reliably participate in telephone follow-up because of significant language barriers.
- Participation in another study with an investigational drug within the 30 days preceding and during the present study.
- Previous enrolment into the current study.
- Enrolment of the investigator, his/her family members, and other dependent persons.</td></tr>
</table>

Screening, recruitment and consent

Information material for KIDS-STEP for participating sites includes posters placed in the waiting areas of the emergency department and a short informational film that is currently in development. A KIDS-STEP website will further be created with public and member-only areas. Any information material reviewed and endorsed by the relevant ethics committee will be deposited in the publicly accessible area of the KIDS-STEP website.

Eligible children are identified in the emergency department when the decision to admit for CAP has been made by the treating physician. A screening log is kept at each site to document all children admitted for CAP. All children are assessed against the inclusion and exclusion criteria as listed above, and are considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria. There are no exceptions to eligibility requirements at the time of randomisation. Eligibility is reviewed and documented by an appropriately qualified member of the investigator's study team (a clinician or nurse who has been trained in study procedures and has been delegated the responsibility by the site PI) at each participating site before children are randomised into the study.

Written informed consent for the child to enter into the trial and be randomised must be obtained from the parent or guardian and where appropriate the participant after explanation of the aims, methods, benefits and potential hazards of the trial and before any trial-specific procedures are performed. Consent may only be obtained once eligibility has been confirmed. The English-language version of the participant information and informed consent form is available as an online supplement to this article. A trial register is kept at each site listing the trial ID numbers to be used. The date of randomisation is added to the register.

Randomisation and blinding

Treatment assignment is sequential, through the dispensation of trial medication. Centre-specific randomisation lists were prepared in advance following a big stick design with a maximum tolerated imbalance of three patients.[15] Randomisation lists were constructed by an independent statistician at the clinical trials unit (CTU) of the University Hospital Basel and conveyed to the Pharmaceutical Unit at the University Hospital Basel, which prepared the trial medication. Randomisation lists are kept concealed at

the trial pharmacy. Each bottle has a unique code and this is entered into the trial database under the participant's trial ID.

Blinding is ensured through the use of placebo, which is indistinguishable from the active treatment in any way but the active ingredient. All caregivers (including nurses, treating physicians), the patients and their parents, the investigators, the outcome assessors and the data analysts are blinded to the allocated treatment.

We envisage optimal blinding because the active drug is a product not widely used in Switzerland with very little advance knowledge of the aspect, taste and texture of the product and individual patients are receiving either active treatment or placebo with no cross-over.

Outcome measures and assessments

The co-primary outcomes are:

- The proportion of children clinically stable at 48 hours after randomisation in the active treated group (oral betamethasone for 2 days) as compared to the control group (placebo) (efficacy).
- The proportion of children with CAP-related readmission within 28 days after randomisation comparing oral betamethasone and placebo (safety).

Clinical stability is defined as the clinician assessing the child as being ready for hospital discharge and/or recorded normal respiratory rate, heart rate and oxygen saturation. Children discharged before 48 hours after randomisation are assumed to be clinically stable at 48 hours as per last clinician assessment. For respiratory rate and heart rate, at least two consecutive age-related normal values as specified in the American Heart Association Accredited Pediatric Advance Life Support documentation is taken to indicate stability. Arterial oxygen saturation in room air of 92% or above measured by pulse oximetry is considered normal.

CAP-related readmissions are recorded by active surveillance at participating centres and in addition identified through parental reporting.

Additional outcomes (table 3) are captured to further evaluate the efficacy and safety of adjunct oral steroids in the management of childhood CAP.

Table 3: Secondary outcomes

Time to hospital discharge after index hospitalisation in days
Time away from routine childcare and/or pre-school/school (for participating children) and away from work (for parents) in days up to 28 days after randomisation
Total antibiotic exposure in days up to 28 days after randomisation
Total duration of hospitalisation in days up to 28 days after randomisation
Proportion of children (re)treated with antibiotics after discharge for any reason at 28 days after randomisation
Proportion of children admitted to intensive care during the initial hospitalisation and up to 28 days after randomisation
Proportion of children experiencing solicited side effects of the trial treatment and/or serious adverse events
Duration of individual moderate-severe CAP symptoms in days assessed by a telephone questionnaire at week 1, 2 and 4 after randomisation
Mortality up to 28 days after randomisation

Trial visit and contact schedules are prepared for each child at randomisation and children are followed on that same schedule until the final follow-up visit regardless of adherence to trial medication. The schedule defines visit times (with windows) necessary for data collection. On overview of trial contacts is given in figure 2.

Sample size and power

A simulation approach was used to estimate the sample size required. Each sample size $n_{i=1,\ldots,43}$= 580, ..., 748 was evaluated by simulating 9999 times n_i individual patients. Events were simulated once for the proportion of 48 h clinically stable patients and once for the rate of CAP-related re-admission, from binomial distributions assuming the two event types are correlated with a correlation coefficient ρ. For each simulation run, each co-primary objective was tested with a two-sided type-I error level of $\alpha = 0.05$. Since the trial's success is defined as showing a successful result in both co-primary endpoints, no correction for multiplicity is required.

To test the superiority of the active treatment arm over the placebo arm with regards to the proportion of patients achieving clinical stability within 48 h, Pearson's $\chi 2$ test with Yates' continuity correction was applied in each simulation run. To examine the influence of the actual difference in rates on sample size,

simulations were performed with effect sizes (absolute difference $\pi_{stability-A} - \pi_{stability-P}$) ranging from 5 to 15%.

To test the non-inferiority of the active vs the placebo with regards to hospital re-admission rates, we constructed in each simulation run the 1-α % confidence intervals (CI) for the difference in rates, using a continuity-corrected modification of Wilson's score method.[16] Non-inferiority was determined if the upper bound of the confidence interval lay below the specified non-inferiority margin δ = 7%. The chosen non-inferiority margin was based on clinical relevance and decided by the investigators.

Assuming an absolute difference of 10% between study arms in terms of the first co-primary endpoint, it was assumed that 80% and 70% of children will achieve clinical stability within 48 hours in the active and placebo arms, respectively. In addition, it was assumed that CAP-related rehospitalisation within 28 days is 5% for both study arms. Finally, it was assumed that the correlation between both endpoints is 0.8, which simulations showed to be the most conservative assessment, leading to the highest sample size (Figure 3).

Under these assumptions, 700 patients need to be recruited to the study – for both arms combined – to ensure 664 patients for the non-inferiority test, while allowing 5% of drop-out.

The incidence rates of the co-primary endpoints are difficult to estimate in advance. A substantial deviation from the assumed rates may lead to an inappropriate sample size due to the critical dependency of the sample size estimation on the assumed rates. To counter this problem, a sample size re-estimation [17] will be performed in a blinded manner once a substantial proportion of the patients have been recruited and information of both co-primary endpoints has been collected. The blinded sample size re-estimation (often referred to as an internal pilot design) allows adjusting the sample size in case the actual rate of events differs substantially from the assumptions taken.

For the sample size re-estimation, the overall (i.e., not treatment arm specific) rates of achieving clinical stability and of re-admission will be estimated in a treatment-blind fashion. The sample size estimation procedure, as described above, will be repeated with the updated assumptions. If, based on the newly collected data, a larger sample size is required for the study, the overall sample size will be increased to the new number, preserving the study's power. If the newly calculated sample size is smaller or equal to the originally calculated sample size, no changes will be made in the study's sample size.

The sample size re-estimation will be performed after 80% of the patients have been recruited and data of both co-primary endpoints collected, or after a seasonality peak in recruitment is finished (i.e. spring) and at least 65% of patients have been recruited. Recruitment may be extended if the sample size re-estimation suggests that an increased sample is necessary.

Analysis plan

The analysis will be performed by the trial statistician using the R language and environment for statistical computing (version 3.6 or higher). Reporting will follow the CONSORT guidelines.

The All Randomized Set (ARS) will consist of all patients randomized to the study; protocol violations will be disregarded in this data set.

The Complete Follow-up Set (CFUP) will consist of all patients randomized to the study who were not lost-to follow-up after 28 days; patients with major protocol violations will be excluded from this set.

The study has two co-primary endpoints, each analysed separately:

Stability rate: The proportion of children achieving clinical stability within 48 h post randomisation

Readmission rate: The proportion of children readmitted to hospital within 28 days post randomisation.

The treatment is declared successful upon showing success for both endpoints together. Each endpoint will be analysed and tested separately using a type-I error rate level of $\alpha = 0.05$.

Rates of achieving clinical stability will be calculated for each study arm, and the risk difference between them reported with 95% CI. A logistic regression model will be fit with study arm as fixed predictor to compare the odds of achieving clinical stability between the study arms. An odds ratio (OR), risk differences and respective 95% CIs will be presented. The superiority analysis will be performed on the ARS and based on the intention to treat principle (ITT).

To test the non-inferiority of the active treatment compared to placebo treatment with regards to re-admission rates, the 95% CI of the difference between the two rates ($p_{readmission\text{-}A}$ - $p_{readmission\text{-}P}$) will be calculated and compared to the predefined non-inferiority margin ($\delta = 7\%$). Non-inferiority of the

treatment will be declared if the upper bound of the 95% CI is smaller than the non-inferiority margin. The non-inferiority analysis will be performed on the CFUP set based on the principle that this is the more conservative approach in a non-inferiority analysis.

If substantial deviations of the analysis as outlined in these sections are needed for whatever reason, the protocol will be amended. All deviations of the analysis from the protocol or from the detailed analysis plan will be listed and justified in a separate section of the final statistical report.

Careful trial planning and conduct minimises the occurrence of missing data as far as possible.

For the ARS, missing values will be replaced by multiple imputation using chained equations based on pre-defined baseline characteristics.

The analyses described above of ARS data will be performed on each imputed data set, and results combined using Rubin's rule for multiple imputation.

As a sensitivity analysis, the primary analysis will be repeated for each of the co-primary endpoints using the alternative analysis set: for superiority using the CFUP, and for non-inferiority using the ARS.

A detailed analysis plan for all secondary objectives will be finalised before the trial's data base closure and will be under version control at the Clinical Trial Unit, University of Basel.

Ancillary and sub-studies

Substudies will have their own analysis plans which will be finalised before the respective databases are locked.

Ancillary study – Impact on nasopharyngeal microbiology: Given the expected immunomodulatory effects of adjunct corticosteroids, different patterns of change in viruses and bacteria in the airways may be observed in children exposed to betamethasone and placebo. This ancillary study will therefore evaluate changes in the presence and load of viruses and bacteria in the nasopharynx during adjunct corticosteroid treatment, comparing baseline and pre-discharge nasopharyngeal samples.

Substudy 1 - Exhaled air pneumonia diagnostics: Definitive identification of a causative agent in childhood CAP is hindered by the fact that significant samples cannot generally be obtained from the lower airways and the relevance of pathogens detected in upper airways secretions is not always clear. This substudy will therefore evaluate a novel non-invasive diagnostic method (mass spectrometry of exhaled air) to determine the relationship between pathogen identification in nasopharyngeal samples by polymerase chain reaction (PCR) and mass spectrometry of exhaled air.

Substudy 2 – Antibody-secreting cell (ASC) response to infection: Determining the causative pathogen of childhood community-acquired pneumonia (CAP) is complicated by the low yield of blood cultures and difficulty obtaining specimens from the lower respiratory tract of children.[18] Therefore, clinicians attempt to detect potential pathogens in upper respiratory tract (URT) specimens. However, PCR of URT samples and IgM serology are unreliable in differentiating infected patients and carriers suffering from CAP caused by several pathogens.[18 , 19] We recently demonstrated that the detection of pathogen-specific IgM antibody-secreting cells (ASCs) using the enzyme-linked immunospot (ELISpot) assay differentiated between *Mycoplasma pneumoniae* infection and carriage.[20] *M. pneumoniae*-specific IgM ASCs were detected only for a few days or weeks after symptom onset, while *M. pneumoniae* DNA in the URT and/or specific IgM in serum persisted for months.[21] Therefore, pathogen-specific ASCs may be an optimal target for determining disease etiology in childhood CAP. The objective of this sub-study is to evaluate the presence and kinetics of pathogen-specific ASCs against several CAP pathogens in patients of the KIDS-STEP study, and to compare ASCs to DNA/RNA load in URT and serum antibody levels.

Substudy 3 – COVID-19: Duration of viral shedding in children tested positive for SARS-CoV-2

Evidence from observational studies in adults showed a longer duration of virus shedding in lower airways after prolonged treatment with steroids during infections with related SARS-CoV-1 or MERS-CoV.[22 , 23] Lower airway shedding has low impact on transmission but extended upper airway shedding would be an important finding for infection control strategies. In children tested positive for SARS-CoV-2 in the upper respiratory tract at admission or during the initial hospitalisation, the proportion of children with persistent detection of SARS-CoV-2 at one and two weeks after randomisation will be assessed.

Substudy 4 – Methodology: Acceptability of and information recall after video-supported informed consent

Audiovisual aids for informing patients, parents and the general public are increasingly used in clinical research.[24 , 25] Although they are widely accepted to be beneficial, little evidence exists on their effectiveness and the way they work. The substudy aims at comparing parental information recall on the key study aspects and assessing the acceptability of the informational video. A standardised questionnaire with 6 knowledge and 3 perception items is added to the telephone follow-up at one week for all parents.

Monitoring

Representatives of the trial management team and a designated external study monitor from the Clinical Trial Unit, University of Basel, conducted a site initiation visit at each study site to inspect the site facilities, verify qualifications of the local investigators and inform the local teams of responsibilities and the procedures for ensuring adequate and correct documentation and use of the electronic data capture system as well as providing training on implementing all trial activities.

In addition, the study monitor will conduct three routine monitoring visits per site, the first after inclusion of 5-10 participants, the second after inclusion of 40-50 participants and the third after inclusion of the last participant, as well as a site closure visit together with representatives of the trial management team at the end of the study to resolve any remaining queries.

The local investigators ensure that source data and documents are made accessible to the study monitor and answer questions posed by the study monitor.

An independent data monitoring committee (IDMC) composed of external experts monitors the accrued data for arising evidence for treatment harm. Additional roles for the IDMC include consideration of implications of arising external evidence for safety and trial continuation, as well as advising on protocol modifications proposed by the investigators.

In accordance with ICH GCP guidelines,[26] audits may be performed by the ethics committee and competent authority during the course of the study.

ETHICS AND DISSEMINATION

Ethical and regulatory compliance

Prior to study conduct, protocol, proposed patient information, consent form and other study-specific documents were approved by the local ethics committee of the trial centre (Ethikkommission Nordwest- und Zentralschweiz (EKNZ), study no. 2018-00563), other local ethics committees in Switzerland for participating sites and Swissmedic (2018 DR 3070).

The study category under Swiss law is class C, i.e. the drug under investigation is not licensed in Switzerland. However, Celestamine® is licensed for medical use in Germany, including recommendations for use in children.

This study is registered on https://clinicaltrials.gov (NCT03474991) and on the Swiss National Clinical Trials Portal (SNCTP000002864).

The study is carried out according to the protocol and with principles enunciated in the current version of the Declaration of Helsinki,[27] the guidelines of Good Clinical Practice (GCP) issued by ICH,[26] in case of medical device: the European Directive on medical devices 93/42/EEC and the ISO Norm 14155,[28] and ISO 14971, the Swiss Law and Swiss regulatory authority's requirements. The CEC and regulatory authorities receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

Patient and Public Involvement

This protocol was written without patient involvement. Patients or guardians were not invited to comment on the study design or to contribute to the writing or editing of this document for readability or accuracy.

Dissemination of results

The data from all centres will be analysed together and published as soon as possible in peer-reviewed journals, as well as being presented at national and international conferences.

The results of this trial will be submitted for Open Access publication in high impact peer-review journals likely to be read by health professionals in the management of CAP in children in Europe. The work will be presented at key medical conferences. To maximise the impact of the trial across Europe, its findings will be disseminated more widely through abstracts for oral and poster presentations submitted to some of the main relevant national and international conferences.

A study website will be developed providing information for collaborators, participants and the public, with the results of the trial eventually posted here. The social media presence of the organisations involved will also be used to highlight news about the trial.

For the main results of the trial a press release will be produced, in collaboration with the press office of the journal publishing the results, which will be distributed to Swiss and European media, to encourage press coverage. This will enable a wider audience to be reached.

TRIAL STATUS AND DISCUSSION

The first participant was enrolled in October 2018. Currently, 141 children have been enrolled in the trial. Follow-up has been completed for 138, with the remaining three still being within the four-week follow-up interval. Recruitment accrual is at 36% of target, mainly due to (1) late/stepwise opening of several study sites, (2) slow performance in the first winter season, and (3) complete absence of recruitment during the COVID-19 lockdown in Switzerland (March to April 2020). Between December 2019 and March 2020 actual recruitment has exceeded pre-trial projections. Recruitment is projected to be complete in late 2021. There has not been any loss to follow-up. Until publication, no emergency unblinding of any participants occurred.

Only few small trials have addressed the potential impact of oral steroid treatment in CAP during childhood.[5] Nagy et al. reported a significant reduction in fever duration (2 vs. 4 days) and length of stay (11 vs. 16.5 days) in children with severe CAP receiving methylprednisolone for 5 days compared with children receiving placebo in a randomised trial with 59 participants.[29] A randomised trial comparing adjunct dexamethasone or methylprednisolone against standard of care (no placebo) planning to enroll 40 participants was being set up but has been withdrawn prior to recruitment (NCT01631916).[30] A placebo-controlled randomised trial of adjunct corticosteroids in CAP complicated by pleural effusion and/or empyema with 56 participants has been completed (NCT01261546),[30] but has not yet reported on its findings. An observational analysis using propensity scores found that adjunct corticosteroids were associated with a shorter hospital stay only in children also receiving beta-agonist therapy, concluding that any benefit might only be seen in children with acute wheezing.[31] At the same time, children without beta-agonist therapy experienced longer hospital stays and increased rates of readmission when treated with steroids in this study. However, 1/3 of children with steroid treatment received long-term medication for asthma, and both ICU admission and invasive ventilation were significantly more frequent in the steroid group. The stratified analysis comparing steroid effects between beta-agonist co-treatment positive and negative children was unadjusted for these factors, leading to the conclusion that the steroid group may have consisted of subgroups of (a) asthmatic children, that would respond well to steroids, and (b) non-asthmatic children that were more severely ill than children not treated with steroids and that would be less likely to be co-treated with beta-agonists. Thus, the different effect of steroids in children with or

without treatment with beta-agonists may simply reflect very different patient groups with different decision criteria for steroid treatment. A subgroup analysis in another retrospective study with 2000 children with CAP found that the risk for treatment failure, defined as switch to another antibiotic therapy regimen than initially prescribed, was higher in non-asthmatic children with CAP when treated with adjunct steroids.[32] However, in this subgroup only 5% of children received steroids and again residual confounding is likely to limit the conclusions that can be drawn. All in all, there is a lack of RCTs with sufficient power and high external validity to provide a definitive answer to the question of the effect of adjunct steroids in children hospitalised with CAP. Betamethasone was selected as the investigational drug because it is the steroid most widely used in respiratory conditions in the trial setting. A 2016 Cochrane review on steroids in asthma identified only one comparative trial on the use of different steroids in children.[33] There was no difference in effect of relative strength adjusted doses of dexamethasone and prednisolone. Betamethasone and dexamethasone have comparably high glucocorticoid activity. We therefore expect the findings to be transferable to the use of lower potency steroids.

In contrast to previous trials, we chose clinical stability at 48 hours as the endpoint for superiority. Clinical stability is relevant to patients and their families as a prerequisite for hospital discharge and can have considerable socioeconomic impacts on the child and parents by allowing a return to normal activity for the whole family. A rapid recovery with no respiratory problems and no need for supplemental oxygen represents directly patient-relevant components of this outcome.

The average length of stay of hospitalised children with CAP is 2 days and by 3-4 days more than 75% of children with this diagnosis have been discharged home.[34 , 35] This reflects the relatively rapid recovery of children with CAP compared to adults. An early assessment of clinical stability at 48 hours has therefore been selected to be of main interest.

Following WHO's recommendation to not routinely administer steroids in patients with suspected or confirmed COVID-19 we were initially facing concerns on whether to keep the trial open during the pandemic. Russell et al. reviewed the evidence on use of steroids in relation to COVID-19 and concluded that the evidence at the beginning of the pandemic did not support steroid administration.[12] The only paediatric evidence included in this review was a study on RSV and corticosteroids and it showed neither a beneficial nor a detrimental effect.[36]

The RECOVERY Trial provided evidence for a benefit of steroids in hospitalised COVID19-patients.[37] Although this trial did not exclude children, the average age of participants was around 65 years and only few paediatric patients were included. While this evidence is not yet sufficiently conclusive to support routine administration of corticosteroids to paediatric COVID-19 patients, it is clear that their use may be an important adjunct therapy for the disease.

Paediatric CAP is a common condition with diverse aetiology. Although lethality in high-resource settings is low, an adjunct therapy reducing length of hospital stay and shortening the duration of symptoms has a high potential to reduce strain on healthcare resources and improve children's and parents' wellbeing. The KIDS-STEP trial will provide conclusive evidence on the effectiveness and safety of steroids for this purpose.

STATEMENTS

A. contributorship statement

JAB and JVDA are co-chief investigators and devised the trial concept with input from SB. JAB, JVDA and UH secured the trial grant. JAB, JVDA, UH, MKV and RS designed the clinical trial. PMMS, ML, KK and TW contributed to the trial design and materials. MC provided statistical input and developed the draft statistical analysis plan. RS provided trial management. MKV wrote the first draft of the manuscript with input from JAB. All authors contributed to subsequent drafts and approved the final version.

B. competing interests

The authors have no competing interests to declare.

C. funding

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D. data sharing statement

The article does not contain a report on analysed data.

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Figure legends:

Figure 1: Trial flowchart

Figure 2: Trial schedule

X* indicates to be collected, if child is still in hospital and until discharge home.

X§ indicates to be collected before discharge home.

(X) indicates tests that may be done if the child's condition requires it or allows it but are not mandatory.

Results will be collected, if available.

X° indicates to be done if visit is face to face.

Figure 3: Required sample size simulations for different strengths of correlation between the primary endpoints

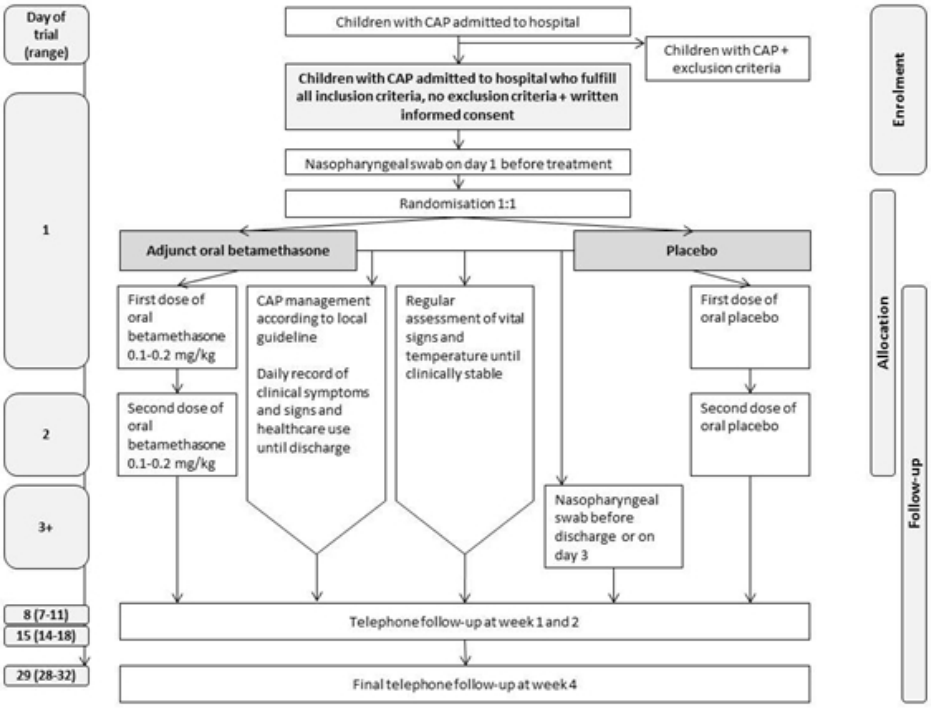


Fig. 1: Trial flowchart

ASSESSMENTS Face to face Telephone Face to face or Telephone Days in trial	DAYS IN TRIAL (telephone follow-up visits -1 to +3 days)								
	Enrol-ment	Rando-misation	Postallocation					Close-out	Unscheduled or End-of-Study visit
		1	2	3	4+	8	15	29	
Trial participation									
Eligibility screen	X								
Parent/Guardian/Child information sheet	X								
Informed consent	X								
Drug supply dispensing		X							
Administration of first dose of trial medication		X							
Administration of second dose of trial medication			X						
Clinical assessment									
Medical history		X							
Physical examination		X							X°
Vital signs and temperature		X	X	X	X*				X°
Symptoms and clinical signs record		X	X	X	X*	X	X	X	X
Concomitant care/healthcare utilisation record		X	X	X	X*	X	X	X	X
Laboratory assessment									
Nasopharyngeal specimen		X			X§				(X°)
Haematology	(X)	(X)							(X)
Biochemistry	(X)	(X)							(X)
Virology	(X)	(X)							(X)
Radiological assessment									
Chest X-ray	(X)	(X)							(X)
Sub-studies									
Diagnostics: Expired air sample			X	X					
Diagnostics: Antibody-secreting cell (ASC) response to infection		X		X				X	
COVID-19: Duration of virus shedding						X	X		

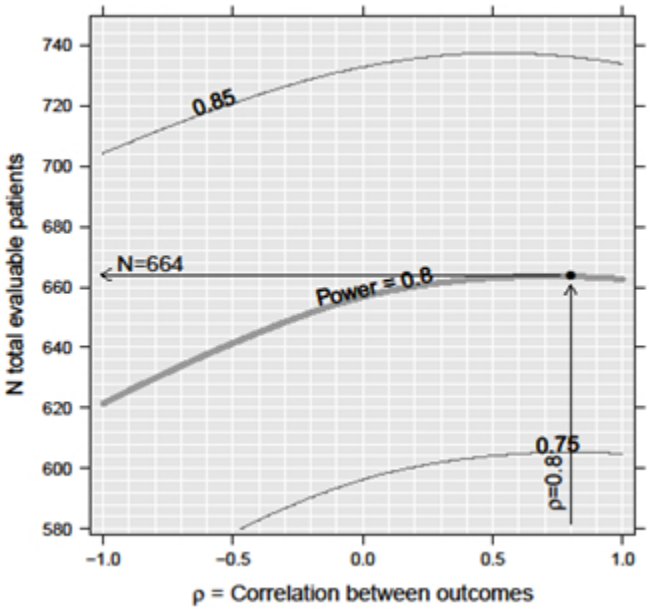


Fig. 3: Required sample size simulations for different strengths of correlation between the primary endpoints

KIDS-STEP Trial

A randomised placebo-controlled multi-centre effectiveness trial of adjunct betamethasone therapy in hospitalised children with community acquired pneumonia

This trial is organised by the University Childrens' Hospital Basel (UKBB) and supervised by SwissPedNet. SwissPedNet is a Swiss network of research institutions that promotes, coordinates and supports research in Child Health.

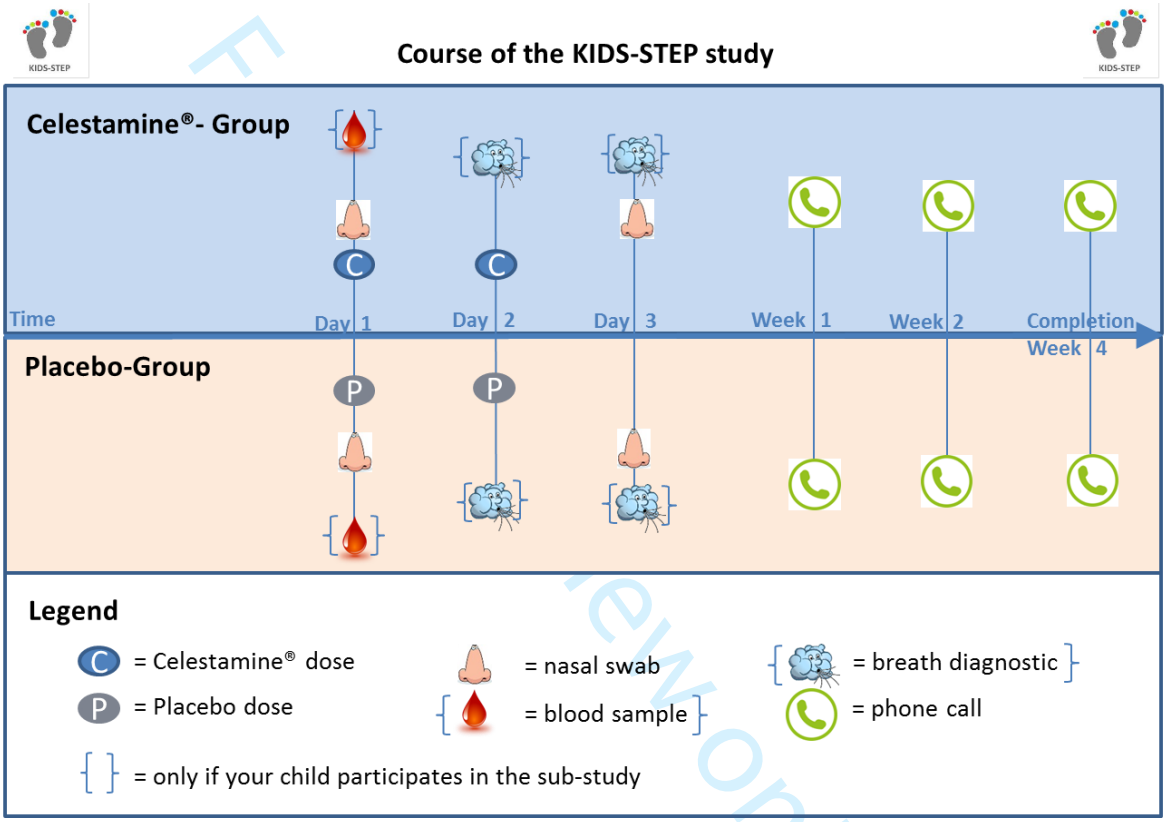
Dear parent or guardian,

We would like to inform you about our clinical trial. Your child is a minor and unable to consent to the planned research activity him- or herself. Therefore we address this information to you and ask you to consider agreeing to your child's participation in the trial. As parents you can consent on behalf of your child.

In this document we will explain the trial to you: First as a brief summary to let you get a general impression, and then as a detailed description.

Summary

1	**Trial aim** The KIDS-STEP trial investigates chest infections in children from 1 year of age that need to be admitted to hospital. A chest infection can be caused by various germs and can be severe enough to cause children to be hospitalised for several days. Even after discharge it will take a few days until children are completely well again. Adults with chest infections get well faster when receiving anti-inflammatory medication (steroids). In children this has not yet been studied. If the effect is similar to that in adults a milder course of disease after hospital admission and a shorter stay in hospital can be expected. In this trial the effect of giving steroids (Celestamine®) in children will be studied and the safety and tolerability of this therapy in children will be confirmed.
2	**Participant selection** In your child a chest infection was diagnosed and an admission to hospital was recommended. We study if we can positively affect the course of disease by adding a steroid (Celestamine®) to your child's treatment. This is why we give you this information sheet.
3	**General trial information** Your child will receive the usual treatment for a chest infection. This is determined independent from the trial. Additionally, in the trial we give a dose of Celestamine® on two consecutive days. Celestamine® is a syrup that is licensed in Germany and that can easily be swallowed by children. The active ingredient in Celestamine® is also licensed in Switzerland but not as a syrup. The active ingredient is commonly prescribed in wheezing or asthmatic children in Switzerland. The KIDS-STEP trial takes place in 8 childrens' hospitals across Switzerland and will involve 700 children from one year of age. The complete duration of the study will be 3 years. The study comprises to groups of the same size (see 4 for details). One group will receive Celestamine® (the active ingredient) and the second group a placebo (a pseudo-medication without active ingredient) of similar look and taste. **Which treatment will my child receive?** Your child will be randomly assigned to one of the groups (randomisation). This means that it is due to chance whether your child will receive Celestamine® or placebo. Neither you nor the trial team can decide which group your child will be assigned to. Celestamine® or placebo will be given in addition to the standard treatment. All children will receive two doses. **What is a placebo?** The placebo looks and tastes like Celestamine®. However, it only contains vehicles and no medically active ingredients. Using a placebo ensures that children in the control group of the trial will be treated the same, because by using a placebo neither the doctor nor the patient can notice a difference between the groups. Being treated the same is important to

	determine the effect of Celestamine®. Neither you nor the trial team will know whether your child will receives Celestamine® or placebo.
4	**Process** If you decide to participate, your child will receive study medication on day 1 and day 2 in addition to the common standard therapy. Depending on which group your child is assigned to they will receive medication with the active ingredient (Celestamine®) or without it (placebo). Independent of group assignment we will take a nasal swab from your child with a cotton bud on day 1 and day 3. In a small group of children – those in whom the new virus causing COVID-19 was detected – additional nasal swabs will be taken at home after 1 and 2 weeks. After 1, 2 and 4 weeks the KIDS-STEP trial team will give you a phone call and ask you a few questions about your child's health and possible side effects of the study medication.  Some hospitals will ask you about your interest in sub-studies in addition to the main study. You can still decide to participate in the KIDS-STEP main trial if you are not interested in the sub-studies. **<u>Sub-study: Exhaled breath diagnostics</u>** This study investigates if it is possible to find the germs causing your child's chest infection in the air your child exhales. For this your child's exhaled breath will be collected twice during the hospital stay and the results will be compared to the findings from the nasal swab. **<u>Sub-study: Diagnosis of atypical germs</u>** This study investigates if it is possible to find a reaction to certain germs in your child's blood. A sample of your child's blood will only be taken if it is anyhow necessary to draw blood from your child for their standard medical treatment.
5	**Benefit** If you decide to participate in KIDS-STEP your child's hospital stay may be shortened by receiving steroids (Celestamine®) and the severity of disease may be lowered. The steroid might also have positive effects on the need for antibiotics and the the occurence of rare complications during the hospital stay. Insights we gain through this trial can help to optimise the treatment of children with chest infections.
6	**Rights** You decide on behalf of your child if they would participate in this trial. This decision has no effect on the medical treatment / care and you do not need to give reasons for this decision.

7	**Duties** If you and your child participate in the trial we ask you to sign the consent and contribute to the trial. This involves answering our phone calls when we ask for your child's wellbeing in week 1, 2 and 4, for example.
8	**Risks** Celestamine® has been in use in Germany for several years. Side-effects when taking it medium-term include raised blood pressure, weight gain and raised blood sugar levels. Following short-term use (less than two weeks) these effects are not expected. As the KIDS-STEP trial involves only two doses of Celestamine® we do not expect serious physical side-effects.
9	**Further treatment options** Celestamine® will be given alongside standard treatment. The trial physician will advise you about further options for your child's treatment.
10	**Results** If new knowledge arises during the ongoing KIDS-STEP trial you will be informed on behalf of your child. Please inform your doctor if you do not wish to be informed.
11	**Confidentiality of data and samples** All legal regulations on data protection will be adhered to and all staff involved are subject to confidentiality. Your child's personal and medical information and the biological samples (nasal secretions, blood etc.) will be processed and stored in a pseudonomised way. Data and samples will be used for other research studies if you give separate consent for this.
12	**Withdrawal** You can decide to withdraw your child from the trial at any time and to stop all participation. Information and samples obtain until this point will continue to be analysed.
13	**Compensation** Your child will not receive compensation for participation in the trial.
14	**Liability** Basler Versicherungs AG, Aeschengraben 21, 4002 Basel will answer for damages incurred.
15	**Funding** The trial is funded by the Swiss National Science Foundation (SNF).
16	**Contact person** Your questions will be answered at any time **Trial director:** Dr. Julia Bielicki, Pädiatrische Pharmakologie und Infektiologie, Universitäts-Kinderspital beider Basel (UKBB), Spitalstrasse 33, 4056 Basel, **Tel. 061 704 12 12 (7 days 24 hours available)** **Local principal investigator:** Prof. Ulrich Heininger, Infektiologie und Vakzinologie, Universitäts-Kinderspital beider Basel (UKBB), Spitalstrasse 33, 4056 Basel, Tel. 061 704 29 09 **Contact local trial team:** Ambulantes Studienzentrum (ASZ) Universitätskinderspital beider Basel (UKBB) Regina Santoro, Spitalstrasse 33, 4056 Basel, **Tel. 061 704 28 54** **Email: kidsstep@ukbb.ch**

Detailed Information

We invite you and your child to participate in the KIDS-STEP trial:

Before you decide if your child will participate, it is important that you have enough information on why we run this trial and what participation means for you and your child. Please do not hesitate to ask the local trial team if something is not clear to you or if you need more information. Thank you for reading this trial information. Should you decide to participate, we will ask you to sign a written consent.

1. Trial aim: How should chest infections in children admitted to hospital be treated best?

The aim of the KIDS-STEP trial is to investigate if anti-inflammatory medication (steroids) positively affect the severity of illness in children with lower airway infections (chest infection, pneumonia). This will be investigated in children admitted to hospital with a chest infection who receive standard therapy.

The KIDS-STEP trial investigates if we can observe
- **less severe disease**
- **a shorter duration of illness**
- **a shorter hospital stay**
- **less complications**

in children who receive steroids.

Currently, steroids are not part of the standard treatment for children who are in hospital with a chest infection. Trial results from adult medicine, however, show that adults with chest infections benefit from treatment with steroids. For children, scientific data confirming this benefit are still lacking. The KIDS-STEP trial tests this in children to improve the treatment of children with chest infections during their hospital stay. In the context of the new viral disease COVID-19 that can lead to a chest infection in some people, the World Health Organization has highlighted the importance of studies investigating the effect of steroids. Children with COVID-19 are therefore invited to participate in KIDS-STEP. Additionally, we would like to find out if steroids influence the length of time that the virus can survive in the nose.

In the KIDS-STEP trial steroids are given in by using the drug Celestamine®. Celestamine® contains the active ingredient betamethasone from the substance group of corticosteroids. Corticosteroids are anti-inflammatory, anti-allergic and immuno-suppressive (by inhibition of the immune system). Betamethasone is used in children in Switzerland for inflammatory skin conditions, allergic reactions, auto-immune diseases and in airway and lung diseases (severe acute asthmatic attack and croup). Celestamine® is licensed in Germany and is routinely used in children with allergic reactions and certain inflammatory conditions.

2. Participant selection: Why is my child being approached?

Participation is open to all children who are admitted to hospital for a chest infection and who are between 6 months and 14 years of age and weigh between 5 and 45 kilograms.
Children are prohibited from participation if they suffer from a severe chronic condition (e.g. mucoviscidosis), have a severe complication (e.g. a large fluid collection in their chest) or if they are known to be allergic to betamethasone or any additional ingredients in Celestamine®.

3. General information: What will happen in the KIDS-STEP trial?

KIDS-STEP is a randomised, placebo-controlled and double-blind trial. This means that the participating children are randomly split into two groups (Celestamine® group and placebo group) (see figure 1). Children in the Celestamine® group receive medication that contains the active ingredient and children in the placebo group receive medication that does not contain an active ingredient. Your child will be randomly assigned to one of the groups (randomisation). This means that it is due to chance whether your child will receive Celestamine® or placebo. Neither you nor the trial team can decide which group your child will be assigned to. The chance to be assigned to each group is the same (50%).

Using a placebo ensures that children in the control group of the trial will be treated the same, because by using a placebo neither the doctor nor the patient can notice a difference between the groups. Being treated the same is important to determine the effect of Celestamine®. Neither you nor the trial team will know whether your child will receives Celestamine® or placebo. The placebo looks and tastes like Celestamine®. However,

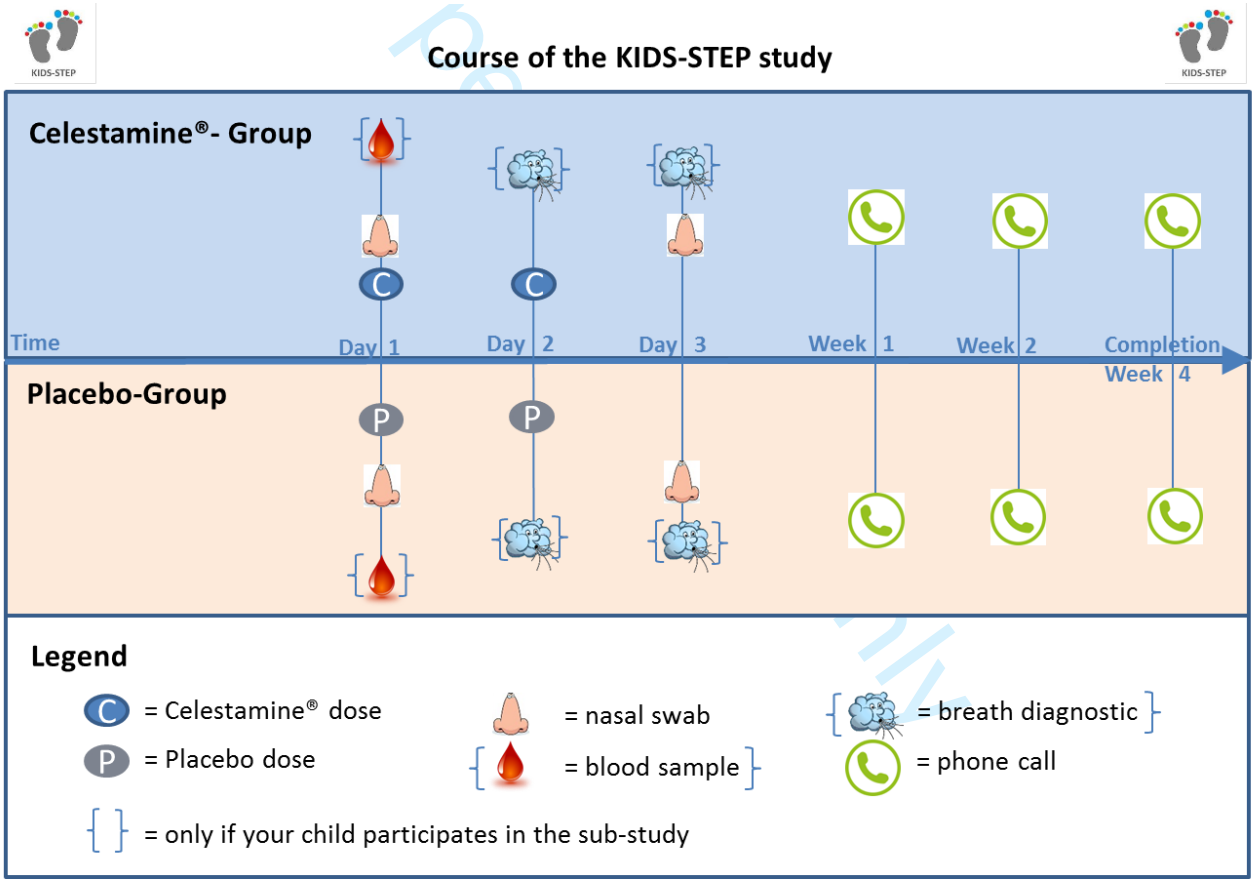
it only contains vehicles and no medically active ingredients, so that neither you nor the doctor can tell the difference. All technical terms will be explained in detail in the glossary (section 17).

Celestamine® is a drug licensed in Germany that is most commonly used in acute treatment of insect bites and auto-immune diseases. In KIDS-STEP children receive a single dose of 0.2 mg per kilogramm body weight on two consecutive days. This dosing regimen conforms with the dose and application in paediatric medicine. Celestamine® is a syrup that can easily be swallowed by children.

Depending on severity there are various standard treatments for chest infections in (e.g. oxygen supplementation, antibiotics). These will be given to all children irrespective of participation in the trial according to the treating physicians assessment. Children taking part in KIDS-STEP will additionally to standard therapy receive the study medication (Celestamine® or placebo).

The KIDS-STEP trial is conducted in compliance with Swiss law. Furthermore, all internationally recognised guidelines are respected. The responsible ethics committee and Swissmedic have reviewed and approved the trial. A description of the trial can also be found on the website of the Federal Office of Health: www.kofam.ch.

4. Process:



Trial participation for your child will last for 4 weeks in total. For KIDS-STEP, **no** additional hospital visits and **no** additional investigations except the nasal swab are necessary. The overall KIDS-STEP trial will take 3 years to complete. Over this period of time 700 children will take part across Switzerland. 90 children from each participating hospital will take part.
The trial KIDS-STEP is embedded in the research network SwissPedNet. SwissPedNet coordinates and supports high-quality research in child health. All large childrens' hospitals and University Childrens' hospitals will contribute to KIDS-STEP. KIDS-STEP will take place at 8 Swiss paediatric departments (multi-centric trial).

For how long will my child be in the trial?

After regular discharge from hospital a trial team member will call you 1, 2 and 4 weeks after joining the trial and will ask you a few questions about your child's health and wellbeing. After the call in week for your child's participation ends.

Which examinations and investigations will be done in my child?

Irrespective of group allocation a nasal swab will be taken from every participating child on day 1 and 3. For this a cotton bud will be placed in your child's nose for a few seconds to collect nasal secretions. These nasal secretions can then be tested in the lab for viruses and bacteria that can be associated with lower airway infections. If the new disease COVID-19 is found in your child in the regular test that are not part of the trial (routine tests) we will instruct you how to collect two more nasal swabs at home (after 1 and 2 weeks) and how to send them to us by mail. We would like to take an additional blood sample from all children that have bloods drawn for their routine medical care. In a few children exhaled breath will be collected during the hospital stay on two consecutive days.

5. Benefit

Chest infections are a common reason for children having to stay in hospital. Based on already known information on the effect of steroids in chest infections, the severity of illness may be reduced by Celestamine® and the hospital stay may be shortened. In children, there is no significant data for the beneficial use of steroids in lower airway infections yet. This is why we would like to evaluate this in our trial. If your child participates in this trial they can possibly benefit in form of a milder course of illness and a shorter hospital stay. The results from this trial can be important for other children who also have a chest infection.

6. Rights

Participation in the trial is voluntary. If you as parents / guardians decide that your child will not participate in the trial or if you withdraw from participation at a later time, you do not have to explain why. Medical treatment and care are guaranteed irrespective of your decision and are not influenced by your decision. Questions regarding trial participation may be asked at any time. Please contact the person named at the end of this information.

7. Duties

If you and your child participate we ask you to sign the consent and to actively contribute to the trial. This includes answering the phone calls on your child's wellbeing in weeks 1, 2 and 4. We ask you to inform the trial team and physician about the continuation of your child's illness. Please tell them if new symptoms, new complaints or changes in your child's condition arise. Please also let the KIDS-STEP trial team know about concurrent treatments and therapies at doctors outside the hospital. A notification of new medication that is prescribed to your child is especially important.

8. Risks and burden for participants

Celestamine® has been in use in Germany for many years. Side-effects when taking it medium-term include raised blood pressure, weight gain and raised blood sugar levels. Following short-term use (less than two weeks) these effects are not expected. As the KIDS-STEP trial involves only two doses of Celestamine® we do not expect serious physical side-effects.

Your child will not need any further medication or tests for KIDS-STEP apart from the trial medication and the tests previously mentioned.

In case we ask you to collect additional swabs at home and send these to us, there will be no cost for you, as we will hand out to you all necessary material and a return envelope.

9. Further treatment options

The steroid (Celestamine®) will be given alongside standard care. Your child does not have to participate in this trial. If your child does not participate the standard treatment will be given.

10. Trial results

The trial physician will notify you as parent / guardian about all new insights concerning the KIDS-STEP trial that might influence benefit or safety and therefore the consent for participation. You will also be notified in case of incidental findings (e.g. in nasal swab analyses) that may be relevant for your child's health or may require treatment. If you do not wish to be informed about any of this, please contact your physician.

11. Confidentiality of data and samples

Your child's personal and medical data are collected for this trial. Only very few people working on the trial will see your child's identifiable data – and exclusively to fulfil tasks within the trial. During data collection your

child's data will be pseudonymised. Pseudonymisation means that all identifiable data (name, date of birth etc.) will be deleted and replaced by a code (= key). Only few authorised people can identify your child with the key. All other people are unable to trace your child from the available data. The key always remains at your hospital.

Your child's samples will be stored in a biobank for research. This biobank is held by PD Dr. Adrian Egli,, Head of Clinical Microbiology at Universitätsspital Basel, Petersgraben 4, 4031 Basel.
It is possible that your data and samples will be used for other tests at a later time or that they are sent to another biobank in Switzerland for tests and re-utilisation not yet specified.
We aks you to sign a separate consent for this use at the very end of this document.

It may be necessary for the trial team to request additional information from your child's GP. Only data that is relevant for the trial will be requested, e.g. consecutive treatment by the GP after discharge from hospital.

In rare cases journals in which trial results shall be published require that individual patient data (so called raw data) are tranferred. If individual data will be transferred they will be pseudonymsed at all times. Therefore it will never be possible to identify your child from the raw data.

Everyone who has access to project data is bound by confidentiality. All data protection requirements will be adhered to and names of patients will never be published in an article nor online.

The nasal swabs taken on day 1 and 3 as well as any blood samples from your child will also be stored pseudonymised. Storage will be in a special database (biobank) for research purposes.

It is possible that the trial will be audited by the responsible local ethics committee or the medicines' agency Swissmedic. The trial physician will have to disclose personal and medical data for these audits. In case of any damages it is also possible that a representative of the insurance company or a physician treating your child will have to review these data. All these people are bound by absolute confidentiality.

12. Withdrawal

You can decide to withdraw your child from the ongoing trial and thereby end participation at any time. The pseudonymised data and samples collected until that time will continue to be analysed.

Further investigations or any subsequently planned contact will be discontinued from the time of withdrawal. Data collected until the time of withdrawal will remain pseudonymised. Please consider if you agree with this prior to participation in the trial. By signing the consent it is understood that you agree tot he pseudonymised storage of your child's data also after a withdrawal from the trial.

13. Compensation for participants

Your child will not receive compensation for participation in the trial.

14. Liability

Should your child suffer any damage in connection to the trial the institution that initiated the trial and is responsible for its conduct will be liable. Conditions and procedures are governed by law.

The University Childrens' Hospital Basel has taken out a policy with Basler Versicherungs AG, Aeschengraben 21, 4002 Basel in order to be able to bear any liability in case of damages. Damages caused by a licensed medical product used in accordance with the standard of care, or which arise under placebo treatment or would have occured under application of a standard therapy the same terms of liability apply that apply to treatment outside the trial. If your child has suffered any damage please contact the trial physician or the insurance company named above.

15. Funding

The trial is funded by the Swiss National Science Foundation (SNF).

16. Contact person(s)

For questions, uncertainties or emergencies during or after the study you can contact one of these people at any time.

Local principal investigator:
Prof. Ulrich Heininger, Infektiologie und Vakzinologie, Universitäts-Kinderspital beider Basel (UKBB), Spitalstrasse 33, 4056 Basel, Tel. 061 704 29 09

Trial director:

Dr. Julia Bielicki, Pädiatrische Pharmakologie und Infektiologie, Universitäts-Kinderspital beider Basel (UKBB), Spitalstrasse 33, 4056 Basel, Tel. 061 704 12 12 **(7 days 24 hours available)**

Contact local trial team:
Ambulantes Studienzentrum (ASZ) Universitätskinderspital beider Basel (UKBB)
Regina Santoro, Spitalstrasse 33, 4056 Basel, Tel. 061 704 28 54
Email: kidsstep@ukbb.ch

17. Glossary (terms worth explaining)

- What is a „placebo“?
  Some people who take medication will not get better due tot he medication itself but due to the doctor’s attention and care. This can be distinguished when they get better even after receiving pseudo-medication. This pseudo-mediation looks like true medication and hast he same packaging but it actually does not contain an active ingredient. It is called a „placebo“.
  Sometimes one part of the participants of a clinical trial will be treated with the true medication and the other part with such a placebo. This makes is possible to better evaluate on comparison how good the active ingredient actually works or if the improvement is only caused by attention and care. Also, improvement is sometimes just the natural course oft he disease.

- What does „randomised“ mean?
  In many trials two or more different ways of treatment are compared. For example, true medication is compared to a placebo. In this case, two groups of participants are formed – one gets the true medication and the other one the placebo. „To randomise“ then means, that a draw will decide who becomes part of which group. In a test like this it is due to chance if someone receives the true medication or placebo.

- What is meant by „single-blind“ or „double-blind“?
  A trial is „blinded“ (single or double) to obtain better and more precise results. A trial is called „single-blind(ed)“ if in a trial either the participants or the researchers whether a participant receives the true medication or the placebo. A computer will draw who receives which.
  A trial is double-blind if neither the participants nor the researchers know whether a participant receives the true medication or the placebo. After the end of the trial the „blinding“ will be broken. In case of an emergency, „blinding“ can also be broken earlier.
  A person who knows that they receive the true medication and not a placebo will observe their body’s reactions very differently from someone who knows that they only receive a placebo. This may lead to people who take the true medication overestimating the medication’s effect compred to those people only receiving a placebo.

- „double-blind, randomised, placebo-controlled trial“:
  The trial investigates how wellt he new medication works. For this, participants will be split into (usually) two separate groups: participants in one group receive the medication under investigation, participants in the other group a placebo (i.e. a pseudo-medication that looks like proper medication but does not contain an active ingredient).

Informed consent

Written informed consent for participation in a clinical trial

Please read this form thoroughly. Please ask if you do not understand anything or if you like to know something. Your written consent is necessary for the patient's participation in the trial.

BASEC number:	2018-00563
Study name:	A randomised placebo-controlled multi-centre effectiveness trial of adjunct betamethasone therapy in hospitalised children with community acquired pneumonia (KIDS-STEP trial)
Responsible institution:	Dr. Julia Bielicki, Pädiatrische Pharmakologie, Universitäts-Kinderspital beider Basel (UKBB), Spitalstrasse 33, 4056 Basel
Trial location:	UKBB, Basel
Local member of trial team: Surname, name and role in print:	Prof. Ulrich Heininger, Infektiologie und Vakzinologie, Universitäts-Kinderspital beider Basel (UKBB), Spitalstrasse 33, 4056 Basel
Participant: Surname and name in print: DOB:	d d m m y y y y ☐ female ☐ male

- As parent / guardian of the patient named above, I was informed verbally and in writing at the location of the trial about the purpose and course of the trial, about possible advantages and disadvantages and about potential risks.
- I confirm that in the interest of my child I decide that my child will participate in this trial. On behalf of my child I accept the verbal and written information. I have had enough time to deliberate this decision.
- My questions concerning this trial have been answered. I will keep the written information and a copy of the infomed consent.
- I agree that the patient's GP will be notified of participation in the project.
- I agree that responsible professionals from the trial sponsor, the responsible research ethics committee and the medicines agency Swissmedic are allowed to review the patient's personal and identifiable data for audit and monitoring purposes under strict confidentiality.
- I know that personal data (and samples) may only be transferred pseudonymised and for the purpose of research.
- In case of ongoing medical treatment at a site different from the trial site I authorise the subsequent medical team to transfer records relevant for the trial to the local trial physician.
- On behalf of the patient I can withdraw participation at any time and without explanation. This will not result in any disadvantage for the patient's medical care. All information and samples obtained until that time will continue to be used for analysis of the trial.
- I have been informed that insurance is in place for damages incurred as a result of trial participation.
- The duties named in the information are to be fulfilled. In the interest of health the trial physician can exclude the patient from the trial at any time.

Place, date	Surname and name (print) Relationship to the patient (e.g. mother / father): Signature relative / legal guardian / parent

Confirmation by the member of the trial team: I hereby confirm that I explained the character, meaning and consequences of the clinical trial to the relative / legal guardian / parent of the participant. I assert that I fulfil all legal obligations concerning the trial. Should I learn of any aspects during the conduct of the trial that might influence the participant's willingness to participate in the trial I will notify the relative / legal guardian / parent without delay.

Place, date, timet	Surname, name and role of the trial team member obtaining consent (print) Signature of the trial team member

Consent for:

Re-utilisation of pseudonymised biological material and (genetic) personal data for research purposes (Art. 29 HFV)

Surname und name of patient / person concerned:
Date of birth:

I hereby consent to biological material and genetic data from my child that is derived from this study, the medical care or other sources may be re-utilised for research purposes in pseudonymised form.

I permit the re-utilisation of my child's genetic data and samples from this study for medical research. The samples will be stored in a biobank and will be used for non-specified future medical research. This consent does not expire.

I understand that the samples will be pseudonymised and the key will be stored securely. Data and samples can be can be sent to other databases and biobanks in Switzerland and abroad if these adhere to the same standards as in Switzerland. All legal requirements concerning data protection will be adhered to.

My decision is voluntary and can be revoked at any time. If I withdraw my child's genetic data will be anonymised and the samples will be destroyed. To revoke my decision I need only notify my trial physician and I do not need to give an explanation.

Usually all data and samples will be analysed and results published in an aggregated way. Should a result be found that will be important for my health I may be contacted by my trial physician. I will let my trial physician know if I prefer not to be contacted.
If results from data and samples will be commercialised I will not be able to claim a share in the commercial use.

Place, date	Surname and name (print) Relationship to the patient (e.g. mother / father): Signature relative / legal guardian / parent

Place, date	Surname, name and role of the trial team member obtaining consent (print) Signature of the trial team member

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
☑Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
☑Trial registration lines (ll) 324-5	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Not included Protocol version	3	Date and version identifier
☑Funding funding statement, ll430ff	4	Sources and types of financial, material, and other support
☑Roles and responsibilities	5a auth or list	Names, affiliations, and roles of protocol contributors
	5b ackn owle dge ment s	Name and contact information for the trial sponsor
	5c ackn owle dge ment s	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities

	5d acknowledgements	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
☑Background and rationale	6a ll 52-89	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b ll 143-149, 388-393	Explanation for choice of comparators
☑Objectives ll 74-89	7	Specific objectives or hypotheses
☑Trial design ll 91-93, fig. 1	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
Methods: Participants, interventions, and outcomes		
☑Study setting ll 104-106	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
☑Eligibility criteria table 2	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
☑Interventions	11a ll 94-96, table 1	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b n/a	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)

	11c not deailed	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d ll 95-96	Relevant concomitant care and interventions that are permitted or prohibited during the trial
☑Outcomes ll 151-174, figure 2	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
☑Participant timeline figure 2	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
☑Sample size ll 176-217	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
☑Recruitment ll 116-128	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

☑Allocation:		
Sequence generation ll 136-142	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism ll 136-142	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation ll 136-142	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
☑Blinding (masking)	17a ll 143-149	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how

	17b not detailed	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
☑Data collection methods	18a ll 97-99, 157-165, table 2	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b ll 171-174	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Partially included Data management	19 ll 301-307	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
☑Statistical methods	20a ll 219-253	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b ll 252-253	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c ll 246-251	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
☑Data monitoring	21a ll 308-311, acknowledgements	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	21b n/a	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
☑Harms ll 164-5, figure 2, table 3	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
☑Auditing 312-313	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

☑Research ethics approval abstract, 317-323	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Not included Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
☑Consent or assent ll 129-132	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Not included Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
☑Declaration of interests competing interests statement	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Not included Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Not included Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
☑Dissemination policy	31a ll 337-350	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions

	31b not detailed	Authorship eligibility guidelines and any intended use of professional writers
	31c not detailed	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
☑Informed consent materials supplement	32	Model consent form and other related documentation given to participants and authorised surrogates
☑Biological specimens ll 258-262, fig. 2	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.