1. Title Page

Title	TARGET-EU: Effectiveness of nirsevimab for RSV-lower respiratory tract infection hospitalization in infants ≤12 months of age
Research question & Objectives	The primary objective is to assess the effectiveness of nirsevimab (50 mg or 100 mg based on weight > or < 5kg) in infants (≤12 months) for preventing hospitalisation due to RSV-lower respiratory tract infection compared to infants not receiving nirsevimab
Protocol version	V1.0
Last update date	18 March 2026
Contributors	**Primary investigators contact information:** Dr. Elisa Barbieri, Prof. Anna Cantarutti **Contributor names:** Dr. Riccardo Boracchini, Prof. Ian Douglas, Prof. Daniala Weir
Study registration	**Site:** https://catalogues.ema.europa.eu/node/4440/administrative-details **Identifier:** EUPAS1000000539
Sponsor	**Organization:** EU PE&PV research network **Contact:** eupepv@uu.nl
Conflict of interest	Elisa Barbieri salary is currently supported by Ministero dell'Istruzione, università e ricerca (MIUR).

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2. Abstract

Background

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infection (LRTI) in infants, associated with considerable morbidity and hospitalization. Before nirsevimab introduction, palivizumab was the only licensed preventive measure in Italy, restricted to high-risk infants (including those ≤35 weeks gestational age, chronic lung disease, congenital heart disease). Nirsevimab, a recombinant monoclonal antibody approved by EMA in September 2022, provides sustained protection throughout the RSV season with a single dose by binding to the RSV F protein and preventing viral entry. While systematic reviews demonstrate nirsevimab effectiveness (odds ratio 0.17 95% CI 0·12–0·23; I2=85·8%, for RSV-related hospitalization), most real-world evidence comes from Spain, France, and the US, with only one small Italian regional study. This evidence gap necessitates locally contextualized effectiveness estimates within the Italian healthcare system.

Objectives

The primary objective is to assess nirsevimab effectiveness in preventing RSV-LRTI hospitalization within six months of administration among infants ≤12 months compared to no immunization. Two estimands are defined: Estimand 1 evaluates effectiveness under a hypothetical scenario where control group participants would never receive nirsevimab, while Estimand 2 applies a treatment policy strategy, evaluating effectiveness regardless of subsequent nirsevimab receipt in controls.

Methods

This study employs the target trial and the estimand frameworks using Italian electronic health records (2023-2025) from PEDIANET, a population-based database capturing primary care, hospitalizations, immunizations, and prescriptions. Exposed infants are those receiving nirsevimab (ATC code J06BD08); controls are unexposed infants. Inclusion criteria: age <12 months at exposure, born at ≥29 weeks gestational age. Exclusion criteria: ongoing LRTI infection, maternal RSV vaccination during pregnancy, or palivizumab eligibility. Time zero for exposed infants is the first nirsevimab administration date; controls are matched 1:1 on age group (≤3.0, >3.0–≤6.0, >6.0 months) and calendar week of exposure. Follow-up is six months, ending at outcome occurrence, death, transfer out, or study end. The primary outcome is RSV-LRTI hospitalization and confounders include age, sex, prior LRTI episodes, healthcare utilization (visits and antibiotic prescriptions), and area deprivation index, all measured before time zero. Inverse probability of treatment weighting (IPTW) using propensity scores estimated via logistic regression will adjust for confounding. Stabilized weights truncated at 1st and 99th percentiles will be applied in log-binomial regression models to estimate marginal risk ratios. Sensitivity analyses include inverse probability of censoring weighting (IPCW) to address missing-at-random assumptions and tipping-point analyses under missing-not-at-random assumptions. Supplementary analysis allows control participants to contribute multiple times and potentially transition to the exposed group upon nirsevimab receipt.

3. Amendments and updates

Version date	Version number	Section of protocol	Amendment or update	Reason
18 March 2026	1.0		N/A	N/A

4. Milestones

Table 1. Milestones

Milestone	Date
Study protocol for RWD study	08 August 2025
Preliminary results RWD study	April 2026
Final Study report	10 June 2026

5. Background

Respiratory syncytial virus (RSV) is a widespread respiratory pathogen that affects individuals across the lifespan but poses the greatest threat during early childhood. It is the leading cause of acute respiratory illness in infants and is associated with considerable morbidity and mortality.[1] Before the introduction of nirsevimab, the only licensed preventive measure against RSV in Italy was palivizumab, a monoclonal antibody licensed for use in a small subset of the paediatric population (i.e. infants born at ≤ 32 weeks gestational age and up to 6 months of age at the start of the RSV season, those with chronic lung disease and congenital heart disease up to 24 months of age, those with a recent heart transplant, etc) [2] In the population of infants who did not qualify for palivizumab administration, the standard of care did not include any preventive measure and was limited to supportive care in the event of RSV infection. Nirsevimab received EMA recommendation for marketing authorization in September 2022 for the prevention of RSV lower respiratory tract disease in newborn babies and infants during their first RSV season (when there is a risk of RSV infection in the community).

Nirsevimab is a recombinant human immunoglobulin G1 kappa monoclonal antibody that neutralizes RSV by binding to a highly conserved, neutralizing epitope on the prefusion conformation of the RSV F protein. This binding prevents the RSV F protein from mediating fusion between the viral and cellular membranes, which is an essential step for viral entry. Because the medicine is removed slowly from the body, over a period of several months, a single dose of nirsevimab protects infants against RSV disease during the entire RSV season [3]. In the HARMONIE pragmatic trial

nirsevimab efficacy against RSV – LRTI hospitalization in infants <12 months of age was found to be 83.2% (95% confidence interval [CI], 67.8 to 92.0; P<0.001) [4]. According to a recent systematic review, Nirsevimab was associated with a lower odds of RSV-related hospitalisation (odds ratio 0·17; 95% CI 0·12–0·23; I2=85·8%), a lower odds of ICU admission (0·19; 0·12–0·29; 55·6%), and a lower odds of LRTI incidence (0·25; 0·19–0·33; 35·1%) in infants aged 0–12 months [5]. Even if some of the trials were primarily designed to assess RSV-associated medically attended LRTI, and RSV-LRTI hospitalization was a secondary endpoint, these findings are consistent with the pivotal trials of Nirsevimab [4].

Currently, most of the real-world evidence was generated by studies set in Spain, France and the US, with only one study reporting evidence from one small region in Italy. A TTE in the Italian specific health system will generate locally contextualised relevant effectiveness estimates.

6. Research question and objectives

The aim of the study is to evaluate the effectiveness of nirsevimab, compared with no immunization, in preventing RSV-LRTI hospitalization among infants ≤12 months during the six months of following administration.

6.1. Primary Estimand 1

Research question targeted by the estimand 1: Among infants ≤12 months entering their first RSV season, what is the cumulative risk ratio of RSV-LRTI associated hospitalization of a single intramuscular injection of nirsevimab compared to no treatment, while alive, and in the hypothetical scenario where the control group would not receive nirsevimab.

Table 2. Estimand 1

	Target Trial	**Target Trial Emulation**	**Comment**
Population	Infants ≤12 months	Infants ≤12 months	
Treatment Conditions	Intervention group: nirsevimab Control group: No treatment	Intervention group: nirsevimab Control group: No treatment	Exposure to nirsevimab defined based on first recorded administration
Endpoint	Hospitalization for RSV-associated with Lower Respiratory Tract Infection during RSV season within 6 months of start of treatment	Hospitalization for RSV-associated with Lower Respiratory Tract Infection during RSV season within 6 months of start of treatment	Emulated using coded data
Summary Measure	Risk Ratio	Risk Ratio	
Intercurrent events and strategies to handle them	**Intercurrent events** (1) receipt of nirsevimab [only for the control group] (2) death	**Intercurrent events** (1) receipt of nirsevimab [only for the control group] (2) death	Identification of both intercurrent events relies on coded data

	Handling Hypothetical (1) While alive (2)	**Handling** Hypothetical (1) While alive (2)	

Rationale for handling of intercurrent events: In estimand 1, the hypothetical strategy for handling the receipt of nirsevimab in the control group will be used to evaluate the effectiveness of nirsevimab in a hypothetical scenario where receipt of nirsevimab in the control group would not occur.

6.2. Supplementary Estimand 2

Research question answered by the estimand: Among infants ≤12 months entering their first RSV season, what is the cumulative risk ratio of RSV-LRTI associated hospitalization of a single intramuscular injection of nirsevimab compared to no treatment, while alive and regardless of the use of nirsevimab in the no treatment group.

Table 3. Estimand 2

	Target Trial	**Target Trial Emulation**	**Comment**
Population	Same as table 2	Same as table 2	
Treatment Conditions	Same as table 2	Same as table 2	
Endpoint	Same as table 2	Same as table 2	
Summary Measure	Same as table 2	Same as table 2	
Intercurrent events and strategies to handle them	**Intercurrent events** (1) receipt of nirsevimab [only for the control group] (2) death **Handling** Treatment policy (1) While alive (2)	**Intercurrent events** (1) receipt of nirsevimab [only for the control group] (2) death **Handling** Treatment policy (1) While alive (2)	

Rationale for handling of intercurrent events: In estimand 2, the treatment policy strategy for handling the receipt of nirsevimab in the control group can be used to evaluate the effectiveness of nirsevimab regardless of the occurrence of this intercurrent event. This estimand is considered more conservative in showing superiority.

7. Research methods

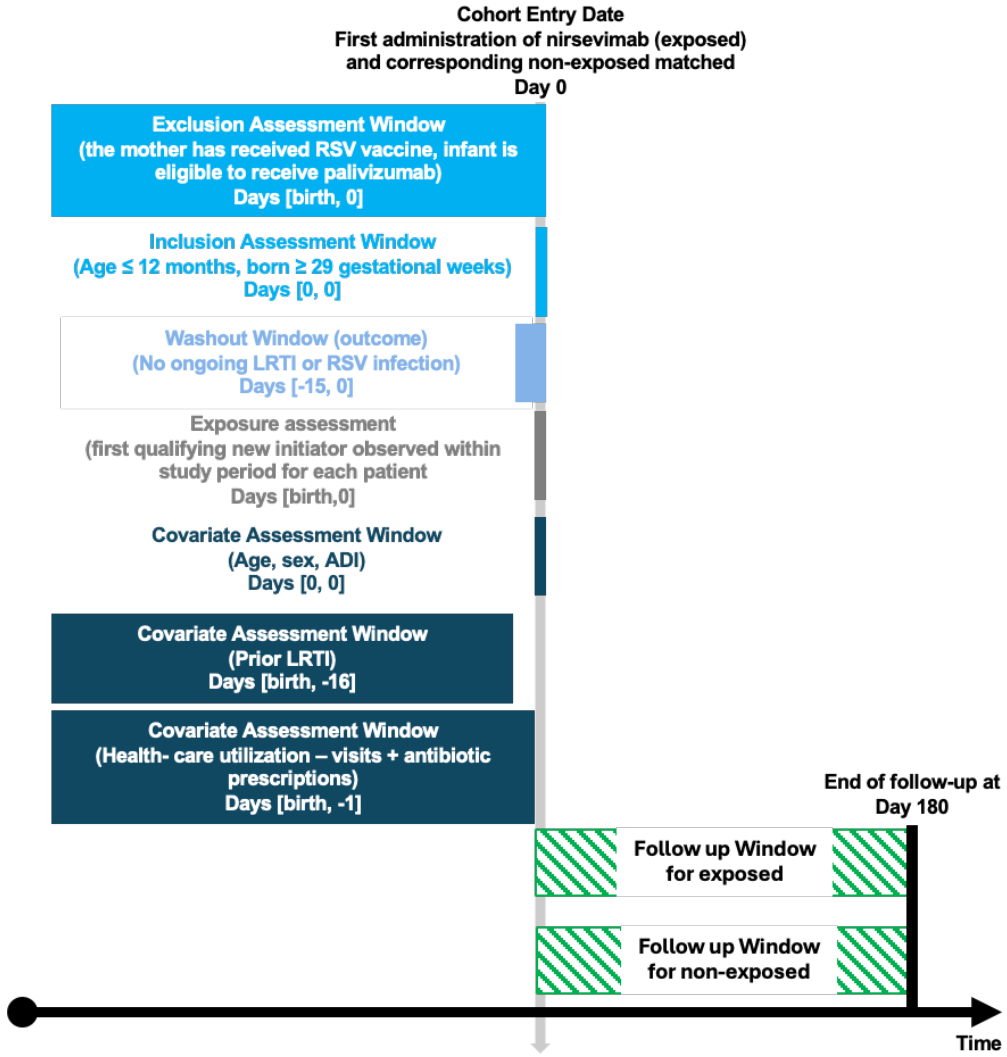
7.1. Study design

Research design (e.g. cohort, case-control, etc.): cohort

Study design choice:

A cohort design is well suited to emulation of the target trial for interventions such as nirsevimab, where the exposure is fixed at a single point in time (i.e. single administration) rather than repeatedly administered. This design aligns with the principles of target trial emulation and avoids some of the additional assumptions required in case–control studies, such as the representativeness of selected controls. Indeed, the main advantage of the cohort design (as opposed to case-control or self-controlled designs for example), is the fact that the cohort design is most similar to the design of a parallel arm trial, thus easing the process of emulation and interpretability. The cohort design allows for risk-based estimates (i.e., risk ratios, risk differences), which are more straightforward to interpret.

7.2. Study design diagram



LRTI = lower respiratory tract infection
RSV = Respiratory syncytial virus

7.3. Setting

This study is conducted using routinely collected electronic health records from 2024 to 2025, reflecting the period of nirsevimab use in routine clinical practice (e.g., primary care and/or administrative databases). The data was collected in routine care and captures immunoprophylaxis administration, prescriptions, health outcomes of interest, and relevant covariates. Data are sourced from Italy, providing population-based and representative coverage of real-world clinical care.

7.3.1 Definition of time 0 (and other primary time anchors) for entry to the study population

In this study:

- For the exposed group, “time 0” is defined as the date of first receipt of nirsevimab during the study period. This date represents the earliest point at which the individual could reasonably be expected to experience any potential effects associated with the intervention. Anchoring “time 0” at the time of administration ensures that follow-up and outcome ascertainment are appropriately aligned with the biologically plausible period of risk or benefit.
- For the comparator group, “time 0” is defined as the date of receipt of nirsevimab for the matched exposed individual. This matching date is selected to mirror the temporal distribution of cohort entry in the exposed group, thereby minimising biases related to calendar time and seasonality (especially relevant in studies involving respiratory pathogens), as well as temporal changes in healthcare delivery or data capture. At time 0, comparator individuals are required to be alive, eligible, and not yet exposed to nirsevimab. Individuals in the comparator group who subsequently will receive nirsevimab during follow-up will be not contribute data to the study after the nirsevimab administration. To emulate a parallel-arm target trial, matching will be performed without replacement at each index date. Individuals can enter the study only once, at their first eligible index date.

Because infants in the unexposed group do not have a treatment administration date, a 1:1 matching procedure will be used to assign a comparable index date (time 0). For each infant receiving nirsevimab, one infant who did not receive nirsevimab will be selected and assigned the same index date, matched on age group at the time of nirsevimab administration (≤3.0 months, >3.0 to ≤6.0 months, and >6.0 months) and calendar week of administration. This matching procedure ensures alignment of follow-up time between exposure groups and accounts for age and calendar time. All subsequent assessments, such as the application of inclusion and exclusion criteria, outcome surveillance, and follow-up duration, are defined relative to this primary temporal anchor.

Table 4. Operational Definition of Time 0 (index date) and other primary time anchors

Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry	Washout window	Care Setting[1]	Code Type[2]	Diagnosis position	Incident with respect to…	Measurement characteristics / validation	Source of algorithm
Exposure nirsevimab	Date of incident administration of nirsevimab (time 0)	Single	Incident	[birth, 0]	IP, OP, ED, Hosp	ATC	N/A	Nirsevimab	No validation study	ATC: J06BD08 in the immunization registry
Non exposure to nirsevimab	Same time 0 as matched nirsevimab user	Single	Incident	[birth,0]	IP, OP, ED, Hosp	ATC	N/A	Nirsevimab	No validation study	ATC: J06BD08 in the immunization registry

[1] IP = inpatient, OP = outpatient, ED = emergency department, Hosp = hospitalization, OT = other, N/A = not applicable

[2]See the appendix for a listing of clinical codes for each study parameter

7.3.2 Study inclusion criteria

1. ≤ *12 months of age* at first exposure to Nirsevimab

   Rationale: We restricted the population only to those ≤ 12 months of age because this is the target population for immunization programs implemented.

2. Born at ≥29 weeks gestational age

   Rationale: We restricted the population only to those born at or after 29 weeks of gestational age because those born before are usually exposed to palivizumab or might have had a previous prophylaxis with palivizumab and then a prophylaxis also with nirsevimab. Table 4. Operational Definitions of Inclusion Criteria

Table 5. Operational Definitions of Inclusion Criteria

Criterion	Details	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Infants ≤12 months of age at first exposure to nirsevimab or matched date for controls.	Difference between month and year of birth and time 0. The study period starts in October. This will be applied after selection of time 0	[0,0]	N/A	month and year of birth	N/A	Exposed Controls	N/A	N/A
Born at ≥29 weeks gestational age	Before selection of time 0	[0,0]	OP	Gestational week	N/A	Exposed Controls	N/A	N/A

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, N/A = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

7.3.3 Study exclusion criteria

1. **Ongoing LRTI infection**

   Rationale: RSV is one of the major causes of respiratory illnesses in infants and the viral testing in LRTI is not recommended as per usual care. Further, the interaction between the monoclonal antibody nirsevimab with anti-RSV antibodies produced by the immune response of the individual is not known. LRTI diagnosis will be grouped in episodes. Any subsequent LRTI diagnosis occurring within 14 days of the initial LRTI diagnosis date will be considered part of the same episode. LRTI will include pneumonia, bronchitis, bronchiolitis, and non-specific LRTI coded diagnosis as reported by the family paediatricians in the clinical notes. LRTI are defined ongoing if t0 falls within the episode.

2. **Infants whose mothers have received RSV vaccine during pregnancy**

   Rationale: Infants have not the same base risk of RSV infection as not immunised or children immunised with monoclonal antibodies.

3. **Infants eligible to receive palivizumab.** We will determine those eligible to receive palivizumab based on demographic (gestational age) and clinical condition.

Rationale: because we want to focus on nirsevimab. Children eligible to receive palivizumab are infants born at ≤ 35 weeks gestational age and up to 6 months of age at the start of the RSV season and RSV immunization campaign, those with chronic lung disease and congenital heart disease up to 24 months of age, those with a recent heart transplant. Further other eligibility criteria are cystic fibrosis, neuromuscular diseases, craniofacial congenital anomalies, immunodeficiency.

Table 6. Operational Definitions of Exclusion Criteria

Criterion	Details	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Ongoing lower respiratory tract infection or RSV infection	Ongoing symptomatic lower respiratory tract infection is selected because the RSV testing is not always performed at the primary care level and RSV is a common cause of LRTI. The testing is not helpful in initiating the treatment because no specific treatment is necessary for RSV-LRTI. – we will address this exclusion criteria after selection of time 0	[-15,0]	IP, OP, ED	ICD9CM or free text	all	Exposure Controls	Algorithm validation	Machine learning approach, based on discharge letters free text and ICD9CM diagnoses identification algorithm for LRTI validated by clinicians^
The mother has received RSV vaccine during the pregnancy	This event will be measured on the mother; however, it is part of the data collected in the	[birth, 0]	N/A	Yes/no/unknown	N/A	Exposure Controls	No validation study	The Family Paediatricians are surveying the carers about

	clinical files of the infants							vaccination during pregnancy. It is a mandatory information
The infant is eligible to receive palivizumab - Immunodeficiency		[birth,0]	OP	ICD9CM + ATC + exemption from payment codes	all	Exposure Controls	Exposure Controls	Investigator defined composite measure
The infant is eligible to receive palivizumab - Chronic lung disease		[birth,0]	OP	ICD9CM + exemption from payment codes	all	Exposure Controls	Exposure Controls	Investigator defined composite measure
The infant is eligible to receive palivizumab - Chronic heart disease		[birth,0]	OP	ICD9CM + exemption from payment codes	all	Exposure Controls	Exposure Controls	Investigator defined composite measure
The infant is eligible to receive palivizumab - Cystic fibrosis		[birth;0]	OP	ICD9CM + exemption from payment codes	all	Exposure Controls	Exposure Controls	Investigator defined composite measure
The infant is eligible to receive palivizumab - Neuromuscular diseases		[birth;0]	OP	ICD9CM + exemption from payment codes	all	Exposure Controls	Exposure Controls	Investigator defined composite measure
The infant is eligible to receive palivizumab - Craniofacial congenital anomalies		[birth;0]	OP	ICD9CM + exemption from payment codes	all	Exposure Controls	Exposure Controls	Investigator defined composite measure
The infant is eligible to receive palivizumab - born at 29 ≤ x ≤ 35		[0,0]	OP	Gestational week + month	N/A	Exposed Controls	N/A	N/A

weeks gestational age and < 6 months of age at the start of the RSV season and RSV immunization campaign				and year of birth				
The infant is eligible to receive palivizumab - recent heart transplant		[birth;0]	N/A	ICD9CM + exemption codes	N/A	Exposed Controls	N/A	N/A

^ Algorithms are being finalized and will be validated before the analysis implementation

7.4. Variables

7.4.1 Exposure(s) of interest

Exposure to nirsevimab will be defined using ATC codes or free text. As in the target trial, we use unexposed to nirsevimab as the control condition. This assumes a lack of coded Nirsevimab administration accurately reflects non-exposure.

Algorithm to define duration of exposure effect:

Not relevant.

Table 7. Operational Definitions of Exposure.

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
Exposure	Nirsevimab	N/A	[0, 0]	N/A	ATC	N/A	Exposure	Nirsevimab treatment	N/A	ATC: J06BD08 in the immunization registry
Control	No presence of nirsevimab ATC	N/A	[0, censor]	N/A	No presence of ATC	N/A	Controls	N/A	N/A	No presence of ATC: J06BD08 in the immunization registry

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, N/A = not applicable

[2] See appendix for listing of clinical codes for each study parameter

[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

7.4.2 Outcome(s) of interest

RSV-LRTI hospitalization is the primary outcome of interest. This is a hard outcome that is of great interest to patients, clinicians, and policy decision makers.

Table 8. Operational Definitions of Outcome

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source of algorithm
RSV-LRTI hospitalization	Hospitalization associated with a LRTI and an RSV positive test referred in the medical discharge letter or ICD9-CM codes of LRTI and a test positive for RSV.	Yes	binary	[-15;0]	IP	Internal label	all	Exposure Controls	No validation yet	Machine learning approach, based on discharge letters free text and ICD9CM diagnoses identification algorithm for LRTI validated by clinicians^

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, N/A = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)
^ Algorithms are being finalized and will be validated before the analysis implementation

7.4.3 Follow up

The study follow up is six months which aligns with previous studies and accounts for the RSV seasonality.

Table 9. Operational Definitions of Follow-Up

Follow up start	day 1	
Follow up end[1]	**Select all that apply**	**Specify**
Date of outcome	Yes	See Table 7
Date of death	Yes	Discharged dead or registry recorded death, whichever came first
End of observation in data	Yes	Transfer out recorded
Day X following index date *(specify day)*	Yes	Day 180
End of study period (specify date)	Yes	30 September 2025
End of exposure *(specify operational details, e.g. stockpiling algorithm, grace period)*	No	
Date of add to/switch from exposure *(specify algorithm)*	Yes	Date that infants in the control group receive the treatment (estimand 1 only)
Other date *(specify)*	N/A	

[1] Follow-up ends at the first occurrence of any of the selected criteria that end follow-up.

7.4.4 Covariates (confounding variables and effect modifiers, e.g. risk factors, comorbidities, comedications)

We will adjust for sex, area deprivation index and the occurrence of LRTI episode(s) prior to the nirsevimab administration as well as the healthcare utilization to control for potential confounding and improve comparability between infants who receive nirsevimab and those who do not. These variables are selected a priori based on clinical relevance and their expected association with both the likelihood of receiving nirsevimab and the risk of RSV-LRTI hospitalization.

- Age at t0 will be included as a continuous variable and, where appropriate, categorised to account for potential non-linear associations with both treatment allocation and RSV hospitalization risk. Younger infants are at higher risk of severe RSV disease and may be prioritised for prophylaxis.

- History of prior LRTI before t0 will be included as a binary variable. Previous LRTI episodes may indicate increased baseline vulnerability to respiratory illness and may influence future hospitalization risk. LRTI diagnosis will be grouped in episodes. Any subsequent LRTI diagnosis occurring within 14 days of the initial LRTI diagnosis date will be considered part of the same episode. LRTI will include pneumonia, bronchitis, bronchiolitis, and non-specific LRTI coded diagnosis as reported by the family paediatricians in the clinical notes.
- Healthcare utilisation prior to t0 will be captured using two measures: number of healthcare visits and number of antibiotic prescriptions. These variables will be treated as counts and categorised based on their distribution in the study population. They serve as proxies for underlying morbidity, healthcare access, and health-seeking behaviour, all of which may influence both treatment receipt and the probability of hospitalization.
- Sex will be included as a binary variable. Differences in RSV susceptibility, disease severity, and healthcare utilization by sex have been described. In addition, biological differences in immune response may influence the effectiveness and pharmacodynamic response to monoclonal antibodies such as nirsevimab. Therefore, sex may act as a confounder in the association between nirsevimab exposure and hospitalization.
- Socioeconomic context will be measured using the area deprivation index, included as a categorical variable (quintiles 1–5). This index provides a proxy for socioeconomic status, which may influence exposure risk, healthcare access, and likelihood of receiving preventive interventions.
- Other covariates which could have been considered possible confounders have been dealt with via exclusion criteria, see Section 7.3.3.

All covariates will be measured prior to t0 to ensure appropriate temporal ordering and to avoid adjustment for variables that may lie on the causal pathway between nirsevimab administration and RSV-LRTI hospitalization. These variables will be used in adjustment methods (e.g., regression, weighting, or matching) to emulate the balance of a randomized target trial.

Table 10. Operational Definitions of Covariates

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Age		continuous, categorised	[0; 0]	N/A	N/A	N/A	Exposure Controls	N/A	N/A
Calendar week	Number of weeks from 1 October 2024 to 31 March 2025 in integers starting from 1	Count, categorised.	[0; 0]	N/A	N/A	N/A	Exposure Controls	N/A	N/A

Prior LRTI episodes		binary	[birth, -16]	IP, OP, ED	ICD9CM codes + free text	all	Exposure Controls	No validation	Machine learning approach, based on discharge letters and diagnosis identification algorithm for LRTI validated by clinicians^
Health- care utilization - visits	Number of visits before time 0.*	Count, categorised. Categorisation based on the distribution	[birth, -1]	OP	Visits to the family paediatricians	N/A	Exposure Controls	No validation	N/A
Health care utilization - antibiotic prescriptions	Number of antibiotic prescriptions.*	Count, categorised. Categorisation based on the distribution	[birth, -1]	OP	ATC code	N/A	Exposure Controls	No validation	J01* from medicine prescriptions information
Sex		Binary	[0, 0]	OP	N/A	N/A	Exposure Controls	No validation	N/A
Area deprivation index	Proxy for socioeconomic status.	Categorical (from 1 to 5)	[0, 0]	OP	N/A	N/A	Exposure Controls	No validation	N/A

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, N/A = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)
^ Algorithms are being finalized and will be validated before the analysis implementation
*The quantity will be similarly reassessed before the start of each follow-up period (as described in methods under the estimation of time varying IPCW).

7.5. Core Emulation Table - Design Summary

Table 11. Comparison of Target Trial and Proposed Target Trial Emulation Design Elements

Attribute	Target Trial	Target Trial Emulation	Comment
Eligibility	**Inclusion** - Infants ≤12 months of age at randomisation - Born at ≥29 weeks gestational age **Exclusion** - Ongoing RSV infection - Participation in another RSV prophylaxis trial - No informed consent from the parents - The mother has received RSV vaccine during the pregnancy - The infant is eligible to receive palivizumab	**Inclusion** - Infants ≤12 months of age at index date - Born at ≥29 weeks gestational age **Exclusion** - Ongoing lower respiratory tract infection or RSV infection - The mother has received RSV vaccine during the pregnancy - The infant is eligible to receive palivizumab	Eligibility applied using structured EHR data Operationalised using prescriptions, EHR primary care data and diagnostic codes; will require lookback windows for accurate classification. Ongoing symptomatic lower respiratory tract infection is used as exclusion criteria instead of "RSV infection" as per target trial because testing is not always performed in primary care and RSV is a common cause of LRTI. The testing is not helpful in initiating the treatment because no specific treatment is necessary for RSV-LRTI.
Setting	Multicentre	Routine care data sources (i.e. family care physician practices and linked administrative databases) capturing immunoprophilaxis administration, prescriptions, outcomes, and covariates	Real-world data captures care as delivered; supports pragmatic design Reflects the setting from which patients are most likely to be recruited from. The measurement of characteristics (comorbidities) can be conducted using both inpatient and outpatient information.
Treatment conditions	Intervention: Nirsevimab, 50 mg (<5 kg) or 100 mg (≥5 kg) IM injection once on Day 1 Control: No treatment, no injection	Nirsevimab administration as reported in the immunization registry or relevant regional repository at, 50 mg or 100 mg IM injection once identified with the active product ingredient or the ATC codes (ATC: J06BD08) Control: No treatment, no injection	Relies on accuracy of registry and repository data, which is anticipated to be high.

Treatment Assignment	Participants will be randomised in a 1:1 ratio using stratified randomisation based on age at the time of randomisation (≤3.0 months, >3.0 to ≤6.0 months, and >6.0 months), .	Treatment assignment is based on caregiver decision. Treatment is universally offered after birth and in the primary care setting.	Matching according to 7.3.1. and IPTW used to balance confounders in absence of randomisation; design emulates randomised treatment assignment As randomisation cannot be directly emulated in this observational setting, a 1:1 matching will be conducted. In addition, inverse probability of treatment weighting (IPTW) will be applied at the analysis stage to adjust for other baseline differences (as described in 7.4.4)
Follow-up	Begins at randomisation; ends at first occurrence of outcome, loss to follow-up, death, study withdrawal or 180 days	Begins at first nirsevimab administration (exposed) and matching date with the relative control (unexposed). The follow up ends at outcome of interest, loss to follow-up, death, or 180 days after start of follow up.	Aligns start of follow-up with treatment administration to mimic start of trial
Outcome	Primary outcome: laboratory confirmed RSV LRTI which is defined as a hospitalization with diagnosis of LRTI associated with a positive result for RSV by nucleic acid amplification–based testing (such as PCR or RT-PCR), conducted on a nasopharyngeal or oropharyngeal sample, or other approved sample types (e.g., saliva or sputum).	Primary outcome: Hospitalization associated with a LRTI and an RSV positive test referred in the medical discharge letter or ICD9-CM codes of LRTI and a test positive for RSV.	Relies on accuracy of hospital records
Intercurrent Events and strategies to handle them	Receipt of nirsevimab in the control group is handled with the hypothetical strategy Death is handled with the while-alive strategy:	Receipt of nirsevimab in the control group is handled with a hypothetical strategy using administration records to estimate administration. Death is handled with the while-alive strategy using routinely recorded data for both Estimand 1 and Estimand 2.	Accuracy of nirsevimab administration and ascertainment of death in the electronic health record is anticipated to be high
Loss to follow up	A patient will be classified as lost to follow-up only if they failed to return for the required study visits and their health condition remains	Deregistration from the family paediatrician practice date where recorded or database end	Deregistration from the practice is routinely recorded in PEDIANET.

	unknown despite multiple attempts to contact them.		

Estimand 2

Same as Estimand 1 but treatment policy strategy used to handle the intercurrent event of receiving nirsevimab in the control arm. Follow-up will not end at the occurrence of this intercurrent event.

7.6. Data analysis

7.6.1 Analysis plan

Overview

For **Estimand 1**, the main estimand supporting decision making, we will estimate the relative risk (RR) under a hypothetical scenario in which participants in the control arm would not experience the intercurrent event of receiving nirsevimab. The status of the outcome of interest, RSV-LRTI hospitalisation, of subjects who experience this intercurrent event, will be considered missing. For the primary analysis, the RR will be estimated using an inverse probability of treatment weighted log-binomial regression model including group assignment as the main predictor and age. Sensitivity analyses will be performed to investigate the robustness of the results to assumptions made in the primary analysis.

For **Estimand 2**, a log-binomial regression model will be used as well, including all participants' follow-up as randomised, regardless of receiving nirsevimab in the untreated group.

Supplementary analyses including diagnostic and descriptive assessments to support the main analysis will be conducted to contextualise data and results from the primary analysis. These will include number of RSV-LRTI hospitalisations per treatment cohort, crude incidence rates, weight and propensity score distributions, covariate balance before and after weighting, number of individuals with missing outcome, number of individuals who experience the identified intercurrent events as well as model diagnostics.

An additional supplementary analysis will be produced whereby individuals in the control arm can contribute data multiple times to the control arm and also to the nirsevimab arm after reception of nirsevimab. For this analysis, a log binomial regression model will be fitted including age category as covariate alongside 'treatment indicator', and a subject-level identifier used as a clustering variable, to correct the standard error estimation for the repeated participation of individuals both within the control arm and between the control and exposed arm, weighted by IPTW, to estimate the risk ratio of the hospitalisation for RSV-associated with Lower Respiratory Tract Infection.

7.6.2 Primary Estimand (1) Analysis

i. Objective

The study will estimate the effect of nirsevimab treatment on the risk of hospitalization for RSV-LRTI compared to no treatment. No specific a-priori hypothesis about the magnitude or direction of effect will be tested.

ii. Exposure contrast

Exposure to nirsevimab vs no treatment

iii. Outcome

RSV-LRTI hospitalization

iv. Analytic software:

R, R studio

v. Handling of intercurrent events

Intercurrent events are handled as follows:

- Receipt of nirsevimab [only for the control group]: non-administratively censored at the date of receiving nirsevimab
- Death: administratively censored at death

vi. Outcome Modelling

Log binomial regression model, weighted by IPTW, which contains 'treatment indicator' variable and age, to estimate the risk ratio of the hospitalisation for RSV-associated with Lower Respiratory Tract Infection.

Assumptions of the model

Log-binomial regression model assumptions include

- a binary outcome (RSV-associated hospitalisation with LRTI),
- correct model specification for the outcome model including the log link and other covariates correctly representing the relationship between predictors and risk of hospitalisation.
- independence of observations (each subject contributes one independent outcome),
- no unmeasured confounding,

vii. Confounding Adjustment

Inverse Probability of Treatment Weighting (IPTW)

To adjust for baseline confounding, inverse probability of treatment weighting (IPTW) will be used. Propensity scores—defined as the probability of initiating nirsevimab versus no immunization—will be estimated using logistic regression. The model will include baseline covariates selected a priori as potential confounders, including patient demographics, comedications, and comorbidities. By selecting co-variates a priori based on prior evidence and assumed causal structure of the data-generating mechanism, we will mitigate the risk of data-drive selection bias maintaining statistical validity and a known causal structure. The covariates included are age, prior LRTI, health- care utilization – visits and health care utilization - antibiotic prescriptions before time 0, sex, area deprivation index. The only covariate with missing values might be the area deprivation index. Missing values will be considered as separate category of the variable. Calendar time (administration week) will also be included in the propensity score model to preserve balance achieved at cohort entry.
Stabilised weights will be calculated by dividing the marginal probability of receiving the treatment actually received (i.e., the overall proportion treated in the study population) by the individual's estimated propensity score (i.e., the conditional probability of receiving their observed treatment). Weights will be truncated at the 1st and 99th percentiles to limit the influence of extreme values.
The truncated stabilised IPTW weights will be applied in a log binomial regression model including only the treatment indicator, as adjustment for confounding is achieved through weighting. Therefore, the estimated treatment effect corresponds to a marginal (population-averaged) risk ratio.
To summarize, we will first perform 1:1 matching on age group at the exposed child's nirsevimab date (≤3.0, >3.0–≤6.0, >6.0 months) and calendar time (administration week) to align time zero. The resulting matched cohort will then be analysed using IPTW. The original pair-matching will not be retained in the outcome model; instead, we will re-weight all individuals in the matched cohort and estimate the effect using a weighted model. We will use stabilized weights with truncation, report weighted covariate balance (standardized mean differences) and obtain robust standard errors.

Assumptions Underlying IPTW

- **No unmeasured confounding (**all relevant baseline confounders are included in the propensity score model).
- **Positivity** (each individual has a non-zero probability of receiving either treatment, given their covariates).
- **Correct model specification (**the propensity score model is correctly specified [functional form, covariate inclusion]).
- **Consistency (**each individual's potential outcome under the observed treatment equals their actual outcome).

Diagnostics for IPTW

- Covariate balance: Check that baseline characteristics are balanced across treatment groups after weighting.
    - Evaluate standardized mean differences (SMDs): SMDs < 0.1 will be considered acceptable.
- Positivity check:
    - Evaluate overlap in propensity score distributions between treatment groups (graphically).
    - Plot the distribution of IPTW for each treatment arm (to be conducted before and after truncation)

viii. Missing Data handling

Missing Outcome Data

Missing outcomes may arise either from the implementation of the hypothetical strategy (e.g., individuals in the control arm initiating nirsevimab during follow-up) or from loss to follow-up (e.g., deregistration before the end of follow-up). For individuals in the control arm who initiate nirsevimab during follow-up, outcomes occurring after treatment initiation will not contribute to the analysis and will be treated as missing. Similarly, individuals who are deregistered before the end of follow-up will have missing outcome data.

The primary analysis will assume that outcomes are missing at random (MAR), conditional on treatment group, age group, and additional baseline covariates included in the analysis model. This assumption will be implemented using multiple imputation.

Multiple imputation will be performed using multivariate imputation by chained equations (MICE). The imputation models will include treatment group, age group, baseline covariates used in the analysis model and the binary outcome variable

Imputations of the missing binary outcomes will be generated using logistic regression. The number of imputed datasets will be 100, which should suffice to ensure stable estimates. Each dataset will be analysed separately using the primary analysis model, and estimates will be combined using Rubin's rules to obtain overall effect estimates and standard errors.

Missing Covariate Data

The only covariate with missing values might be the area deprivation index. Missing values will be considered as separate category of the variable.

7.6.3 Supplemental Estimand (2) Analysis

Same as primary estimand but intercurrent events are handled using the following:

- Receipt of nirsevimab [only for the control group]: No censoring

- Death: administratively censored at death

Missing Data handling:

Missing Outcome Data
Subjects who are lost to follow-up will have missing data as their RSV hospitalisation status by month 6 will be unknown.

In the log-binomial regression model, we will assume outcomes are Missing Completely At Random (MCAR). As justification, it is anticipated that only a very small number of patients will be lost to follow up, and we cannot conceive a mechanism for loss to follow up that would be related to either treatment or outcome.

Missing Covariate Data
The only covariate with missing values might be the area deprivation index. Missing values will be considered as separate category of the variable.

7.6.5 Sensitivity Analyses

Table 12. Sensitivity analyses – Inverse Probability of Censoring Weighting (IPCW)
All sensitivity analyses are performed for primary estimand (Estimand 1) only.

Analysis Methods	Individuals whose follow-up ends before completion of the planned 6-month risk window without experiencing RSV-LRTI hospitalization will have incomplete outcome ascertainment. In these individuals, the occurrence of the binary outcome (RSV-LRTI hospitalization within 6 months) cannot be fully assessed because follow-up ends earlier than the fixed risk horizon. Deaths occurring during follow-up (expected to be rare) will be handled consistently with the "while alive" estimand framework. Although the endpoint is binary, the analysis is implemented using a discrete-time modeling framework in which the risk of the outcome is evaluated in monthly intervals up to the fixed 6-month horizon. To address potential bias arising from incomplete follow-up, a sensitivity analyses will be conducted using inverse probability of censoring weighting (IPCW). <u>Inverse Probability of Censoring Weighting (IPCW):</u> • The probability of remaining under observation at each monthly interval will be estimated using baseline (Age class, Prior LRTI, Health- care utilization – visits, Health care utilization - antibiotic prescriptions, sex, Area deprivation index) and time-varying covariates (Healthcare utilization – visits, Health care utilization - antibiotic prescriptions) • Apply IPCW weights in addition to IPTW for treatment. • Use combined IPTW × IPCW weights in the outcome model. Stabilized IPC weights will be estimated in discrete time using monthly intervals up to the fixed 6-month horizon. For each month, we will model the probability of remaining under observation conditional on baseline and time-varying covariates. Stabilized IPCW will be multiplied by stabilized IPTW to obtain final analysis weights. The outcome analysis will be conducted using a pooled discrete-time log-binomial regression model, in which each individual contributes one

	observation per follow-up month until the end of observed follow-up or loss to follow-up The binary outcome will indicate whether RSV hospitalization occurred that month. The model will include a treatment indicator and a categorical month variable to allow for a flexible baseline risk over time. In the absence of a treatment-by-month interaction term, the estimated treatment effect corresponds to a time-constant relative risk over the follow-up period. Predicted monthly probabilities of RSV hospitalization will be obtained from the fitted model under each treatment strategy. Robust (sandwich) standard errors will be used to account for within-individual correlation due to repeated monthly observations. We will use stabilized IPCW, analogous to stabilized IPTW. In discrete time (monthly intervals up to the fixed horizon T), we will model the probability of remaining under observation at each interval. Stabilized IPCW will be constructed at each month t as the ratio of the probability of remaining under observation conditional on baseline covariates, to the probability conditional on both baseline and time-varying covariates. These quantities represent interval-specific weight components. The overall stabilized IPCW at time t will then be obtained as the product of these components across all prior time points, thereby accounting for censoring occurring throughout follow-up. Given that weights are time-varying, their distributions will be examined and plotted at each discrete time point over the course of follow-up, rather than only at baseline. Additionally, weight distributions and covariate balance diagnostics will be reported at relevant time points to assess the adequacy of the weighting procedure. Extreme weights will be truncated at pre-specified percentiles (i.e., 5th and 95th percentiles), and weight distributions and covariate balance diagnostics will be reported.
Assumptions	• Censoring is conditionally independent of the outcome given covariates. • No unmeasured confounding for censoring. • Correct model specification and positivity.
What is Being Varied?	• In the primary analysis, censoring will be assumed to be conditionally independent of the outcome, given treatment group, age, and the absence of RSV-LRTI hospitalisation up to the time of censoring. IPCW explicitly models the probability of censoring based on additional observed time-varying covariates beyond those in the primary analysis. • No need to do multiple imputation
Why (Objective)	• To assess the robustness of the treatment effect, estimate to violations of the MAR assumption made in the primary analysis. • If results are stable across assumptions, confidence increases that findings are not driven by bias (due to censoring).
Strengths	• IPCW adjusts for measured predictors of censoring. • Provides effect estimate under different censoring assumptions from the primary analysis
Limitations	• IPCW is sensitive to model misspecification. • Cannot account for unmeasured factors affecting censoring. • Weighting can increase variance, especially if weights are unstable • Sensitivity analyses rely on varying the assumptions of the primary analysis, but for censoring these assumptions cannot be verified from the observed data; their plausibility can be discussed yet ultimately remains unknown.

Table 13. Sensitivity analyses -Best-worse case scenario

<table>
<tr><td>Analysis Methods</td><td>

Missing not at random: Best/worst case scenario under missing not at random assumption.
For individuals with missing outcome status at 6 months in the primary analysis, the primary analysis will be repeated under four missing-not-at-random assumptions based on the following scenarios applied separately to each treatment group: a) assuming all those individuals experienced the outcome of interest by 6 months, and b) assuming none of them experienced the outcome by 6 months. This equates to the following scenarios

<table>
<tr><th>Scenario</th><th>Exposed Group (Nirsevimab)</th><th>Control group</th><th>Interpretation</th></tr>
<tr><td>1</td><td>Best case (lowest event rate)</td><td>Worst case (highest event rate)</td><td>Maximally favours Nirsevimab</td></tr>
<tr><td>2</td><td>Worst case (highest event rate)</td><td>Best case (lowest event rate)</td><td>Maximally favours Controls</td></tr>
<tr><td>3</td><td>Best case</td><td>Best case</td><td>Optimistic for both groups</td></tr>
<tr><td>4</td><td>Worst case</td><td>Worst case</td><td>Pessimistic for both groups</td></tr>
</table>
These four scenarios represent the four extremes of a tipping-point sensitivity analysis. In a tipping point analysis, multiple imputation is performed for participants with missing RSV hospitalization status at month 6, assuming that the true proportion of subjects experiencing the outcome varies from 0% to 100% separately in each treatment arm.
</td></tr>
<tr><td>Assumptions</td><td>

All or none of the individuals with missing outcome had the outcome of interest
Correct model specification for the primary analysis.

</td></tr>
<tr><td>What is Being Varied?</td><td>

The assumption that missing data occurs at random.

</td></tr>
<tr><td>Why (Objective)</td><td>

To assess the robustness of the treatment effect, estimate to violations of the missing at random assumption made in the primary analysis.
If results are stable across scenarios, confidence increases that findings are not driven by bias (due to the missingness assumption).

</td></tr>
<tr><td>Strengths</td><td>

Sets bound on the extent of maximum possible bias due to missingness not at random

</td></tr>
<tr><td>Limitations</td><td>

Best/worst case scenarios are the most extreme assumptions of the whole range of scenarios that would have been explored under a full tipping point sensitivity analysis.

</td></tr>
</table>

7.6.6 Other Supplemental Analyses

This supplementary analysis aims to evaluate the treatment effect under an alternative design whereby control subjects can contribute data multiple times and can also contribute data to the nirsevimab group after having contributed as controls.
The exposure, outcome and handling of intercurrent event remain as described in Estimand 1.

The outcome model is the same as Estimand 1, except the RR will be estimated with the person-level identifier used as a clustering variable, to correct the standard error estimation for the repeated participation of individuals both within the control arm and between the control and exposed arm.

To construct comparable exposure groups, a 1:1 matching approach with replacement on a daily sequential basis will be used to select unimmunized individuals as comparators. For the comparator group, "time 0" is defined as the date of receipt of nirsevimab for the matched exposed individual. This matching date mirrors the temporal distribution of cohort entry in the exposed group, minimising biases related to calendar time, seasonality, and changes in clinical practice or data availability. At time 0, comparator children must be eligible, alive, and not yet immunized with nirsevimab. In this supplemental analysis, non-exposed individuals may be sampled more than once as comparators, provided they remain untreated at each corresponding time 0. Once immunised, a child is no longer eligible as a comparator but may contribute follow-up to the exposed group from their own immunisation date.

7.6.7 Core Emulation Table – Estimation Summary

Table 14. Core Emulation Table Estimand 1: Estimation Summary

	Target Trial	Target Trial Emulation	Comment
Analysis Method	Log binomial regression model to estimate the risk ratio of hospitalisation for RSV-associated with Lower Respiratory Tract Infection will be used, including all randomised participants.	Log binomial regression model to estimate the risk ratio of hospitalisation for RSV-associated with Lower Respiratory Tract Infection will be used, including all participants assigned through 1:1 age-group matching at the time of nirsevimab receipt. The model will include exposure group and age, and will be adjusted for sociodemographic, clinical, socioeconomic, and pregnancy-related characteristics available at baseline, using inverse probability of treatment weighting (IPTW).	The same outcome model would be used in the target trial and emulation study. IPTW will be used to emulate random treatment allocation in the observational data (emulation study).
Missing Data Assumptions and Methods to Handle	For intercurrent events handled using the hypothetical strategy (receipt of nirsevimab in the control group), outcomes occurring after treatment initiation will not contribute to the analysis. These individuals will therefore have missing outcome data at month 6. Outcome data may also be missing due to loss to follow-up (e.g., deregistration from the family paediatrician practice before completion of follow-up). Missing outcomes will be assumed to be Missing At Random (MAR), conditional on treatment assignment, age group, and other baseline covariates included in the analysis model, as well as absence of RSV-LRTI hospitalisation up to the time of censoring.	For intercurrent events handled using the hypothetical strategy (receipt of nirsevimab in the control group), that is with non-administrative censoring, individuals have missing outcome at month 6. Censoring will be assumed to be conditionally independent of the outcome given treatment assignment, age, and abs ence of RSV-LRTI hospitalisation up to the time of censoring. Similarly, loss to follow-up due to deregistration from the family paediatrician practice will be treated as right censoring. The same conditional independent censoring assumption will apply. Although the endpoint is binary, we use the terminology of censoring to reflect incomplete follow-up rather than classical missing data.	For the primary endpoint, missing data assumptions and handling are the same in both the target trial and the NIS. In the NIS, missing data may occur in one baseline covariate, and if so, this will be handled be creating a separate category, which in practice will lead to no missing values in the covariate.

	Missing outcomes will be handled using multiple imputation under the MAR assumption, allowing all individuals to contribute to the analysis.	Concerning missing data in the covariates, the only covariate with missing values might be the area deprivation index. Missing values will be considered as separate category of the variable.	
Statistical Model Assumptions	Nirsevimab efficacy is assumed constant over time within the period under consideration. Risk of infection is assumed to only be influenced by treatment assignment (consistency/ no interference).	Nirsevimab efficacy is assumed constant over time within the period under consideration. Risk of infection is assumed to only be influenced by treatment assignment (consistency/ no interference). **IPTW Assumptions**: no unmeasured confounding, positivity, correct model specification, consistency	
Sensitivity Analyses	Sensitivity analysis under missing-not-at-random assumptions will be performed.	To account for potential bias due to censoring (i.e. early stop of follow-up at the time of the occurrence of intercurrent events or at the time of loss to follow-up), we will apply inverse probability of censoring weights (IPCW) in a weighted log-binomial regression model. This assumes that censoring is at random, conditional on the selected covariates included in the IPCW model to calculate the weights. In addition, four extreme scenarios of a tipping point sensitivity analysis under missing-not-at-random assumptions will be performed.	An additional sensitivity analyses has been included in the NIS compared to the target trial. In the additional analysis, a different MAR assumption is made from the one made in the primary analysis. In particular, it is assumed missing data are MAR given additional baseline and time-varying covariates.

Estimand 2: Same as estimand 1 but without sensitivity analysis

Table 15. Core Emulation Table Estimand 3: Estimation Summary

	Target Trial	**Target Trial Emulation**	**Comment**
Analysis Method	Same as Estimand 1	Same as Estimand 1	
Missing Data Assumptions and Methods to Handle	Missing data are assumed to be missing at random conditional on treatment assignment and age.	If data are missing due to loss to follow-up, these are assumed to be missing at random conditional on treatment assignment.	
Statistical Model Assumptions	Same as Estimand 1	Same as Estimand 1	
Sensitivity Analyses	N/A	N/A	

7.7. Data sources

7.7.1 Data sources and quality

Rationale for selection and feasibility:

With an approximate estimated sample size of 7,408 individuals and considering that PEDIANET includes data on 24,572 toddlers aged between 28 days and 23 months, and ~ 30K birth every year it offers large, high-quality, population-based electronic health records of the paediatric population in Italy. It provides the required data elements to operationalize the study design, including demographics, diagnoses, prescriptions, immunization registry and hospitalizations. Data extraction and feasibility assessments confirm that the study variables are available with sufficient completeness and temporal coverage to support the research objectives.

Strengths of data source(s):

PEDIANET provides high completeness and reliability for critical variables such as birth, sex, diagnostic codes (ICD-9) and free text diagnosis, and prescription data (ATC codes) and hospital discharge information. The database support validated outcome definitions and have been widely used in pharmacoepidemiologic studies.

Limitations of data source (with potential impact in the study results):

However, the database has several limitations including lacks information about the family environment, including nursery attending.

Additional limitations:

Potentially major: For children born since 2024, it's unclear whether their mothers received RSV immunization during pregnancy.

Minor: The number of bronchiolitis cases tested for pathogens is unknown.

Minor: The exact number of missing gestational age records at birth is not known.

Data Quality:

Pedianet is a national population database that contains anonymous patient-level data of paediatric population who received healthcare from family paediatricians (FPs) in Italy who were part of the PEDIANET network. The network links FPs distributed throughout several Italian regions designated by the Italian NHS, including Friuli-Venezia Giulia, Liguria, Lombardia, Piemonte, Veneto, Lazio, Marche, Toscana, Abruzzo, Campania, Sardegna, and Sicilia.

Primary Care and Paediatric specialist Records and vaccines from public health. The database is maintained and owned by the Società Servizi Telematici Srl. The maintenance of the database is funded through different research projects. Studies carried out to date have been financed by

public bodies (European Commission, Istituto Superiore di Sanità, AIFA, Consiglio Nazionale delle Ricerche, Regione Veneto, Aziende Socio Sanitarie, Istituto Zooprofilattico delle Venezie, etc.), or private groups such as pharmaceutical companies or international research groups.

Table 16. Overall feasibility assessment summary for CS8

RWD source	Sample size estimation form the hypothetical trial protocol	Feasibility assessment *(yes/yes, with limitations/no)*	Rationale for the feasibility assessment	Limitations identified during the feasibility assessment and categorisation	Description of potential impact of the identified limitations on the study results
Pedianet	With an approximate estimated sample size of 7,408 individuals and considering that PEDIANET includes data on 24,572 toddlers aged between 28 days and 23 months, and ~ 30K birth every year.	Yes	Elements with high criticality are available and seem fairly reliable. Data recency of 6 months at extraction, reasonable for the research question . Sample size can be reached.	·Potentially major: For those patients born since 2024, some unknown maternal RSV immunisation is expected. ·Minor: The total number of bronchiolitis tested for pathogens is unknown. ·Minor: Unknown exact missingness of gestational age at birth. ·.	Some under detection of maternal RSV immunisation is expected. However, maternal RSV immunisation is rare in Italy since it is not reimbursed apart from some specific local health units. Previous studies using the same database to analyse paediatric lower respiratory tract infections (LRTIs) did not report the total number of bronchiolitis cases tested for pathogens. This omission may result in an underestimation of the incidence of RSV-associated LRTIs.

Table 17. Metadata about data sources and software

	Data 1
Data Source(s):	Pedianet
Study Period:	Oct 2023- Sept2025
Eligible Cohort Entry Period:	Oct 2023- Apr 2025
Data Version (or date of last update):	N/A
Data sampling/extraction criteria:	Infants <12 months of age in the period October2024-March2025
Type(s) of data:	Primary care record, Hospitalization discharge letters, immunization registry
Data linkage:	N/A
Conversion to CDM*:	Conception CDM
Software for data management:	R, R studio, SAS
HMA data catalogue link	https://catalogues.ema.europa.eu/network/1000000793

7.8. Data management

The study will be conducted in a distributed manner using the UMCU, ARS Toscana and VAC4EU tools, procedures, and pipeline. Figure 2 specifies the data sets (D) and transformation processes (T), programming follows this pipeline, with involvement of different types of experts.

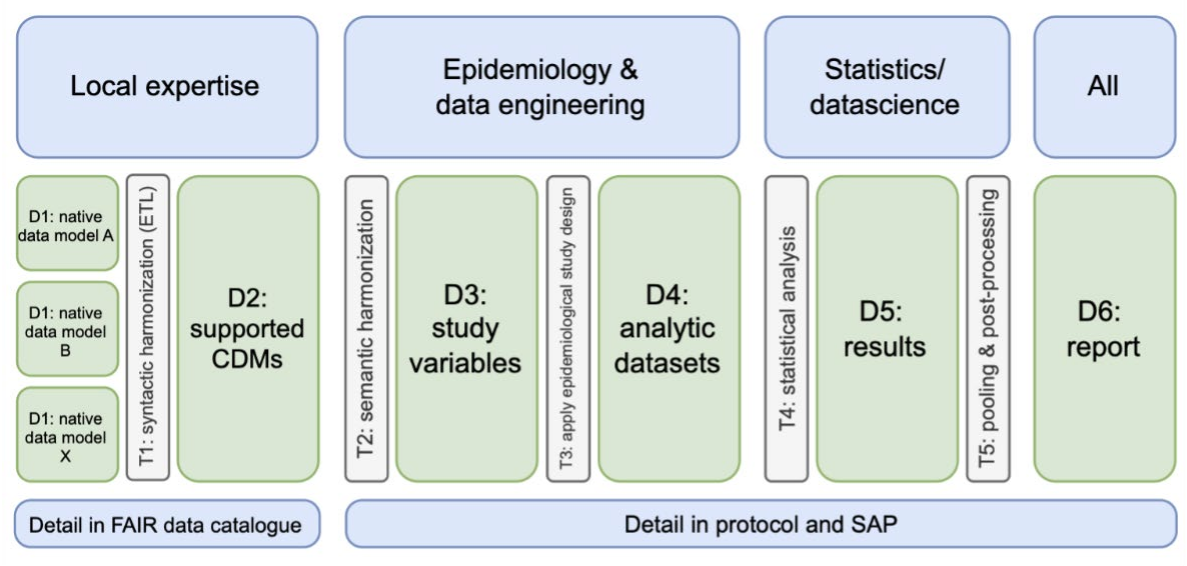


Figure 2. Data Management from the data transformation perspective

D1: Original data can be in any native format

The RWD-RWE pipeline used by VAC4EU starts with data banks that are controlled by the Data Expert and Access Partner (DEAP) and can be in any format. Data always stays local and never leaves the secure environments of the DEAPs. The ETL (extract, transform, load, see below for more details under 'T1') design is shared in a searchable FAIR VAC4EU catalogue. The VAC4EU FAIR Molgenis data catalogue is a meta-data management tool designed to contain searchable meta-data describing organisations that can provide access to specific data sources.

T1: Syntactic harmonisation (ETL)

T1: Syntactic harmonisation is conducted through an extraction, transformation, and loading (ETL) process of native data into the ConcePTION common data model (CDM) (see section 'D2: Common data model'). To harmonise the structure of the data sets stored and maintained by each data partner, a shared syntactic foundation is used. The ETL process has various structured steps as described by Thurin et al (2021):

- DEAPs are asked to share the data dictionaries of their data banks (selected tables and variable names/structure)
- Metadata (descriptive data about the data sources and databanks) & data dictionaries, are uploaded in FAIR data catalogue (Molgenis).

D2: Common data model

For this project, the CDM (D2) is the ConcePTION common data model. The CDM version that is used is v2.2, which is available as an open-source CDM. In this CDM, data are represented in a common structure, but the values of the data remain in their original language (e.g. codes will have either ICD9/10/ICPC/SNOMED or MEDCODEID values).

T2: Semantic harmonisation

During the T2 step, many data transformations occur related to the completion of missing features in the data. Based on the relevant diagnostic medical codes and keywords, as well as other relevant concepts (e.g., medications), one or more phenotype algorithms are constructed (typically one sensitive, or broad, algorithm and one specific, or narrow, algorithm) to operationalise the identification and measurement of each event. In this step we conduct time anchoring (observation periods, look back periods), clean the data such as the dose of vaccines, sort on record level, aggregate across multiple records, and combine concepts for implantation of algorithms, and rule-based creation of study variables.
In this phase of the creation of study variables, semantic mapping is conducted. This semantic mapping across different vocabularies is conducted as part of the R-study script using different functionalities. To reconcile differences between different terminologies and native data availability, machine-readable code lists are used that comprise the terminologies that are used in the network (e.g. ICD-9, ICD10, SNOMED, ICPC and DEAP specific adaptations). This is combined with the BRIDGE metadata file that defines risk windows, look-back periods, and algorithms for each study variable (65,66).

D3: Study variables

D3 datasets are interim data sets with information on study variables for each study participant, the unit may be a person, a medicine, or episode of time. The design of these datasets is described in codebooks. Examples of D3 datasets are the outputs of the ConcePTION pregnancy algorithm, and outputs of functions that define smoking. Multiple functions/packages exist within the VAC4EU, for different study variables.

T3: Application of epidemiological design

In the T3 step epidemiological designs are applied such as sampling, matching (on specific variables and/or propensity scores), and selection based on inclusion and exclusion criteria using the study variables in the D3 datasets. The designs will be implemented for the various study objectives using R-scripts, and these may use the existing functions (R-cran) or functions that have been developed in the VAC4EU community (e.g. matching).

D4: Analytical data set

D4 is an analytical dataset, and multiple D4 data sets may be produced based on the objectives of the study. The format is described initially in a code book for communication between programmers and statisticians.

T4: Statistical analysis

This step in the data transformation pipeline will produce statistical estimates such as descriptives (counts, percentages), distributions (mean, percentiles), rates (prevalence, incidence), regression coefficients, or other relevant estimates. This will be conducted using R.

D5: Results

D5 is the set of estimates, tables or aggregate data that is transferred from the DEAPs to the Digital Research Environment (DRE). The aggregated results produced by these scripts at the DEAP's site will be uploaded to the UMCU DRE for post-processing, pooling and visualisation (Figure 1). The DRE is a cloud-based, globally available research environment where data are stored and organised securely and where researchers can collaborate. The DRE is made available through UMCU. The DRE applies double authentication where researchers can collaborate using data that are stored and organised securely [ref]. UMCU is responsible for data processing and data security.
All researchers who need access to the DRE will be granted access to study-specific secure workspaces by UMCU. Access to the workspaces will be possible only after double authentication using an identification code and password together with the user's mobile phone for authentication. Uploading files will be possible for all researchers with access to the workspace within the DRE. Downloading of files will be possible only after requesting and receiving permission from a workspace member with an "owner" role, who will be a UMCU team member.

T5: Post-processing/pooling

In this step, the result from different DEAPs is pooled and converted into tables and figures for reporting.

7.9. Quality control

All key study documents such as the hypothetical trial protocol, target trial emulation protocol and study reports will undergo senior scientific and editorial review.

Data quality

For all data sources and for each data instance we will conduct *INSIGHT* level 1-2 quality checks, detailed statistical analysis plans for the indicators are available on the public repositories:

- https://github.com/UMC-Utrecht-RWE/INSIGHT-Level1 Hoxhaj, V. (2023). UMC-Utrecht-RWE/INSIGHT-Level1: https://doi.org/10.5281/zenodo.10035167
- https://github.com/UMC-Utrecht-RWE/INSIGHT-Level2 Hoxhaj, V., & van den Bor, R. (2023). UMC-Utrecht-RWE/INSIGHT-Level2: https://doi.org/10.5281/zenodo.10035169

Briefly, level 1 verifies Data Completeness and level 2 Data Consistency.

Level 1 – Data Completeness

The purpose of the level 1 check is to verify the completeness of the ETL process and the data in the variables. Examples of tests are:

- Presence of variables in each of the CDM tables in D2
- Checks for misspellings and letter case in variable names in each of the CDM tables
- Verification of vocabularies
- Check date formats

- Check conventions of values
- Missing data analysis
- Frequency tables for categorical variables

Level 2 – Data Consistency

Real data is not random but follows certain logical constraints that reflect rules governing real-world situations. Examples of indicators generated by level 2 checks are:

- Event dates before date of birth
- Event dates after date of death
- Event dates out of observation periods
- Subjects having an observation but not present in the PERSONS table
- Observations associated with a visit id and occurred before/after the visit start/end date
- Subjects younger than 12 years old reported as parents
- Age at the observation period older than 115 y old Data

Code Quality

These coding practices define how the TARGET programming team collaborates to write clean, reliable, and reproducible code for the VAC4EU Real-World Evidence (RWE) Analytical Pipeline. They aim to ensure clarity, consistency, and maintainability across all case studies within the project.

Coding conventions

To ensure clarity, consistency, and maintainability across the project, the following conventions will be applied to all codebases within the project:

- Consistent style: Code follows a consistent and readable style (see the tidyverse style guide for R).
- Meaningful names: Use clear, descriptive names for variables, functions, and files to convey their purpose.
- Modular code: Break down code into small, reusable functions where possible.
- No hardcoded paths: Use configuration files or relative paths to ensure portability.

Following these conventions makes the code easier to understand, test, and reuse across case studies and teams.

Documenting Code

Code documentation is used to promote good coding practices and ensure our work is understandable, maintainable, and reproducible. To achieve this, we will:

- Use descriptive comments that explain the purpose and rationale behind code sections, focusing on why something is done, not just what.
- Clearly document function inputs, outputs, and side effects, using standardized formats (e.g., roxygen2 in R) where appropriate and supported.

- Write meaningful variable and function names to make the code as self-explanatory as possible.

Version Control

We use Git and GitHub to manage version control. These tools support good coding practices by enabling collaboration, tracking changes, accessing a project's history, and ensuring code quality through review and documentation.
A dedicated GitHub organisation has been created for the project (https://github.com/target-roc19). Each case study is managed in its own repository within this organisation. Repositories are structured consistently across case studies, to reinforce modularity. Access to repositories is controlled through teams.
During development, all repositories remain private to ensure confidentiality. Once the project is finalised, relevant repositories will be made public and assigned a digital object identifier (DOI) via Zenodo to support transparency, reproducibility, and reuse by the wider research community.
To maintain code quality and clarity, we follow the git and GitHub guidelines below.

- Always use pull requests (PRs): never push directly to the main branch.
- Open an issue before creating a new branch. Ideally, one PR resolves one issue to keep changes focused and reviewable.
- Every PR must be reviewed by at least one other person before merging.
- The PR author merges the PR after it has been reviewed and approved.
- Write clear, descriptive commit messages.
- Write informative PR descriptions, including:
    - A concise title
    - Links to related issues
    - A summary of the changes

Continuous Integration

Continuous Integration (CI) is set up to automatically check code quality and run tests whenever changes are pushed to the repository or submitted through a pull request (PR). The CI workflow ensures that the package adheres to predefined style guidelines and that all automated tests pass before changes are merged.

Coding Template

Every case study follows the general coding template used across all code in the TARGET project. The folder structure is organised as follows:

```
case-study-template
|____data
| |____D2_cdm
| |____D3_study_variables
| |____D4_analytic_datasets
| |____D5_results
| |____D6_report
```

|____docs
|____logs
|____run
|____tests
|____transformations
| |____T2_semantic_harmonization
| |____T3_study_design
| |____T4_statistical_analysis
| |____T5_processing_results
|____CHANGELOG.md
|____LICENSE
|____README.md

Project Data Structure and Storage

The data folder follows the Real-World Evidence pipeline structure. Data conforming to the common data model is stored in the D2_cdm folder. Results from transformations T2, T3, T4, and T5 are saved in the respective folders:

- D3_study_variables
- D4_analytic_datasets
- D5_results
- D6_report

Each dataset is associated with a codebook, explained in more detail below.
All data remain securely stored on the Data Expert and Access Partners (DEAPs) servers and are never transferred externally. For testing purposes, dummy datasets are created. These fall into two categories:

- Unit test data: Small, predefined input and output pairs used to test individual transformation steps. These are stored in the tests folder, not in data, and can support automated testing.
- Pipeline test data: Larger, more complex dummy datasets used to test whether the full pipeline runs as expected. These may be included in the repository only if they remain below GitHub's 100 MiB file size limit and will otherwise be shared via SharePoint.

Logging System

When the pipeline is executed, log files are saved in the logs folder. These logs are especially helpful when running the code in the DEAPs environment, as they help trace and diagnose potential errors. We recommend using the logger R package to handle logging throughout the pipeline. A sample logging setup can be found in the logger. R script located at the root of the project directory.

Executing the Analytical Pipeline

The run folder contains scripts used to execute each transformation step in the pipeline.

- A central script, run_pipeline.R, orchestrates the full pipeline from start to finish.
- Subscripts (e.g., run_T2.R or similar) are available to run individual transformation steps separately.

Typically, the run_pipeline.R script is the main entry point used by a DEAP to execute the full pipeline. Before running it in the DEAP environment, the pipeline may need to be adapted to local settings. This can be done using a configuration file that defines variables required to tailor the pipeline to a specific DEAP. Please note that configuration files should not include sensitive information.
Such a file might include variables like:

- The name of the DEAP
- The path to the local data instance
- The path to any required external resources

Testing and Quality Assurance

The tests folder contains scripts to test the analytical pipeline. Tests will be used to ensure code behaves as expected and remains stable over time. By systematically checking inputs, outputs, and edge cases, tests help catch errors early and make future changes safer. We use the testthat R package to structure and run unit tests.
Continuous integration (CI) is used to automate testing. With CI, tests are automatically run each time code is pushed to the repository (e.g., via GitHub Actions). This helps identify issues immediately, ensures that new changes do not break existing functionality, and supports better collaboration by enforcing consistent code quality across contributors.

Modular Data Transformation Workflow

The transformations folder follows the Real-World Evidence pipeline structure. It contains the source code for all transformation steps, which is typically written in R. Each subfolder corresponds to a specific step in the pipeline (e.g., T2_semantic_harmonization, T3_study_design, T4_statistical_analysis, T5_processing_results) and includes the relevant scripts and helper functions for that step.
During the T2 step, a database is usually created (e.g., using DuckDB). This database can be queried using SQL, and it is recommended that all SQL queries be saved as clearly named, standalone SQL script files to ensure readability and reusability.
The purpose of the transformations folder is to structure and modularise the processing logic, making it easier to maintain, test, and reuse across different case studies. By organising code by transformation step, teams can work in parallel, increasing efficiency.

Changelog

A changelog will be kept for all notable changes in the project. Changelogs help track the evolution of the project over time, making it easier for collaborators to understand what has changed between versions. We follow the structure and best practices outlined in Keep a Changelog.

Codebooks

Before developing code, codebooks are created to describe each dataset (D) within the pipeline. A codebook is a comprehensive document that outlines the structure, contents, and metadata of a dataset. It serves as a detailed reference guide for anyone working with the data and plays a crucial role in guiding the development of the analytical pipeline by clearly defining both the inputs and expected outputs.
All codebooks are summarized in a central index file, which provides a high-level overview of the pipeline's structure. For each codebook, the index file includes:

- A brief description of its purpose,
- A list of the scripts used to generate the corresponding dataset,
- A description of the input datasets and input parameters required.

The datasets D2, D3, D4, and D5 are typically subdivided into multiple smaller transformation steps, each detailed within their respective codebooks. These smaller transformation steps ensure that each part of the pipeline is clearly scoped and well-documented.
In addition to supporting development, codebooks help ensure quality control by making transformation logic transparent and verifiable, and they enhance reproducibility by documenting exactly how data is structured and used throughout the analytical pipeline.

Deployment

The analytical pipeline is delivered to DEAPs as a GitHub release, tagged with a version number. Versioning follows the format: vYYYYMMDD.XX, where the date indicates the release date and XX denotes the sub-version or revision number.
Any deployment issues can be reported via the GitHub repository using the issues feature, where the programming team responsible for the R code will collaborate with the local DEAP to resolve them as needed.

Reproducibility

It is recommended to locally use the renv R package to maintain the R version and version of packages for reproducibility purposes.
At this time, however, using renv reliably across different systems and environments remains challenging. For this reason, we currently recommend its use only in local development setups.
We are actively monitoring developments in the R ecosystem related to cross-platform reproducibility. As soon as a more stable and portable solution becomes available, we will revisit this guidance and promote broader adoption.

README Guidelines

Each case study repository includes a README that covers the following points:

- Project Overview: brief summary of the study goals and key research questions.
- Background: context and rationale for the study.
- Repository Structure: Outline of main folders and their contents.
- Data Overview: Description of data sources, formats, and data privacy considerations.
- How to Run: Instructions for running the pipeline and key scripts, plus where outputs are saved.

- Testing: How to run tests to verify code functionality.
- Contributing: Guidelines for code contributions and issue tracking.
- License: Information about the code license.
- Contact: Who to reach out to for help or questions.

Licensing
The code will be made available under an open-source license.

7.10. Study Precision

The sample size for the target trial was calculated to detect an immunization effectiveness of 60%, corresponding to a relative risk (RR) of 0.40, with a two-sided $\alpha = 0.05$ and 90% power ($\beta = 0.10$). Assuming an outcome incidence of 2% in the non-immunized (reference) group, we used a log-binomial model to compare proportions between immunized and non-immunized participants. Under these assumptions, a total of 4,026 participants (i.e., 2,013 per group) would be required to detect a statistically significant difference in outcome incidence. The expected number of events is in the control group.

No hypothesis test will be performed in the non-interventional study emulating the target trial. The rationale of the study size will be based on the precision of the estimation, which is based on the width of the 95% confidence interval. To estimate the 95% CI for a RR from a log-binomial model, the standard error (SE) of the log(RR) is derived from the total number of events.

The sample size obtained in the target trial will be used to calculate the precision with which the RR could be estimated in this non interventional study assuming the same number of individuals will be available in the RWD sources.

We estimated different scenario because of uncertainty in the burden of RSV-LRTI after the introduction of universal immunization for RSV in infants given the possible reduced transmission of RSV.

Assumptions
- Equal allocation to treatment groups.
- Large-sample normal approximation for log(RR).
- Symmetric CI on the log scale.

Table 18. Confidence interval widths under different events counts

Scenario	Events (a / b)	Total Events	SE(log(RR))	95% CI for RR	CI Width	Relative Precision (%)
Full (0%)	23 / 58	81	0.240	0.27 – 0.59	0.32	48%
–10% events	21 / 52	73	0.256	0.26 – 0.62	0.36	58%
–30% events	16 / 41	57	0.301	0.24 – 0.67	0.43	79%
–50% events	12 / 29	41	0.364	0.21 – 0.75	0.54	88%
–70% events	7 / 17	24	0.491	0.17 – 0.93	0.76	132%
–90% events	2 / 6	8	0.816	0.09 – 1.75	1.66	338%

8. Limitation of the methods

Population, Eligibility, and Setting

In the target trial, maternal RSV immunization is a protective factor against RSV-LRTI. In the emulation, this factor is identified from routine healthcare data, where it might be under-recorded. Even though RSV maternal immunization is offered only in some local health units and it is not reimbursed by the national healthcare system, using this variable might potentially misclassify some individuals as with no RSV maternal immunization attenuating comparability with the target trial population. Indeed, individuals born in mothers who received RSV vaccine are at lower risk of experiencing RSV-LRTI.

Treatment Assignment and Follow-up

Randomisation cannot be emulated. Instead, we will match exposed and unexposed participants on key baseline risk factors using appropriate techniques and then complement with IPTW to improve exchangeability and reduce confounding.

Outcomes and Intercurrent Events

Endpoints are identified using validated code lists or algorithms in real-world data sources. Although these definitions are well established, they are not identical to adjudicated outcomes in clinical trials. Misclassification of some variables remains possible, which may bias effect estimates. Where possible, we have used validated algorithms for identifying outcomes (i.e. RSV-LRTI hospitalization), and covariates (i.e. LRTI) to minimize misclassification bias. Using a validated algorithm which will use also free text to identify the primary outcome of interest, RSV-LRTI hospitalization, we will reduce possible misdetection of RSV-positive cases not classified adequately with the diagnostic codes.

Loss to follow-up is defined using practice deregistration or database end, which are proxies for true loss. Although unique patient identifiers mitigate risks of missed de-registration, there remains potential for misclassification (e.g., patients who stop attending their practice but do not formally deregister).

Analysis Methods and Statistical Assumptions

Unlike the target trial, which relied on randomisation to achieve balance, the emulation employs matching and IPTW. This approach requires unverifiable assumptions: no unmeasured confounding, correct model specification, positivity, stable weights, independence of observations. Departures from these assumptions could bias results.
For intercurrent events handled using the hypothetical strategy (receipt of nirsevimab in the control group), that is handled with non-administrative censoring, individuals have missing outcome at month 6. The model assumes missing data are missing at random conditional on treatment assignment and age group. The same assumption is made for data that are missing due to loss to follow-up.
Nirsevimab efficacy is assumed constant over time within the period under consideration. Risk of infection is assumed to only be influenced by treatment assignment (consistency/ no interference).

Missing Data and Censoring

Unlike a trial, where exposure and covariates are actively collected, the emulation must rely on already collected real-world data (i.e., secondary use of data). These differences from trial data collection procedures may affect validity.

Clinical events or conditions are identified through the presence of specific codes or text in the medical record; therefore, if such information is not recorded, the event or condition will be considered not present. Missing information may introduce bias if the probability of missingness is related to patient characteristics or outcomes. In real-world practice, particularly for interventions administered early in life or seasonally, missingness may depend on observed baseline and time-varying covariates that may not be fully captured in the available data.
In the main analysis, missing outcome data will be assumed to be Missing At Random (MAR) conditional on treatment assignment, age group, and other baseline covariates included in the analysis model. Under this assumption, missing outcomes will be handled using multiple imputation, allowing all individuals included at baseline to contribute to the analysis. Sensitivity analyses will be conducted to assess the robustness of results to departures from the MAR assumption.

Generalizability

Limitation: The study population may not be representative of all individuals eligible for the intervention (e.g., due to inclusion/exclusion criteria or data availability), which could limit external validity.

Mitigation: We will describe the characteristics of the study population in detail. Where possible, subgroup analyses will be conducted to explore effect modification and support inference in more specific populations.

9. Protection of human subjects

This is a non-interventional study using secondary data collection and does not pose any risks for individuals. The data source research partner will apply for an independent committee review according to local regulations. Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants. Patient information This study involves data that exists in an anonymized structured format and contains no patient personal information. All parties will comply with all applicable laws, including laws regarding the implementation of organisational and technical measures to ensure the protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

Patient consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from individuals is not required.

10. Reporting of adverse events

The requirements provided in this Module do not apply to non-interventional post-authorisation studies conducted by organisations such as academia, medical research charities or research organisations in the public sector. These organisations should follow the local requirements as regards the submission of cases of suspected adverse reactions to the competent authority in the Member State where the reaction occurred. However, where a study conducted by one of these organisations is directly initiated, managed, or financed by a marketing authorisation holder, or where its design is controlled by a marketing authorisation holder (voluntarily or pursuant to obligations imposed in accordance with Article 21a and 22a of Directive 2001/83/EC, or Article 9(4) and 10a of Regulation (EC) No 726/2004), the requirements provided in this Module are applicable.

11. References

1. Munro APS, Martinón-Torres F, Drysdale SB, Faust SN. The disease burden of respiratory syncytial virus in Infants. Curr Opin Infect Dis. 2023;36(5):379-384. doi:10.1097/QCO.0000000000000952
2. https://bur.regione.veneto.it/BurvServices/pubblica/Download.aspx?name=4_Allegato_DDR_4_12-01-2016_316357.pdf&type=7&storico=False (Accessed on 07-07-2025)
3. https://www.ema.europa.eu/en/documents/overview/beyfortus
4. -epar-medicine-overview_en.pdf (Accessed on 07-07-2025)
5. Drysdale SB, Cathie K, Flamein F, et al. Nirsevimab for Prevention of Hospitalizations Due to RSV in Infants. N Engl J Med. 2023;389(26):2425-2435. doi:10.1056/NEJMoa2309189
6. Sumsuzzman DM, Wang Z, Langley JM, Moghadas SM. Real-world effectiveness of nirsevimab against respiratory syncytial virus disease in infants: a systematic review and meta-analysis. Lancet Child Adolesc Health. 2025;9(6):393-403. doi:10.1016/S2352-4642(25)00093-8