

101034339 – PROMISE

Preparing for RSV Immunisation and Surveillance in Europe

WP3 –Clinical validation studies

D3.4 Final study approvals package for Study 1 and 2

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Definitions

- **Participants** of the PROMISE Consortium are referred to herein according to the following acronyms:
 1. **UEDIN.** The University of Edinburgh (United Kingdom)
 2. **UMCU.** Universitair Medisch Centrum Utrecht (Netherlands)
 3. **UA.** Universiteit Antwerpen (Belgium)
 4. **Imperial.** Imperial College of Science, Technology and Medicine (United Kingdom)
 5. **UOXF.** The Chancellor, Masters and Scholars of the University of Oxford (United Kingdom)
 6. **THL.** Terveystieteiden tutkimuskeskus (Finland)
 7. **RIVM.** Rijksinstituut voor Volksgezondheid en Milieu (Netherlands)
 8. **NIVEL.** Stichting Nederlands Instituut voor Onderzoek van de Gezondheidszorg (Netherlands)
 9. **TUCH.** Varsinais-Suomen Sairaanhoidopiirin Kuntayhtymä (Finland)
 10. **TEAMIT.** TEAM IT Research, S.L. (Spain)
 11. **ReSViNET.** Stichting Resvinet (Netherlands)
 12. **SSI.** Statens Serum Institut (Denmark)
 13. **SERGAS.** Servizo Galego de Saúde (Spain)
 14. **PENTA.** Fondazione PENTA - For the treatment and care of children with HIV and related diseases - ONLUS (Italy)
 15. **FISABIO.** Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (Spain)
 16. **MLU.** Martin-Luther-Universitaet Halle-Wittenberg (Germany)
 17. **SP.** Sanofi Pasteur, S.A. (France)
 18. **GSK.** GlaxoSmithKline Biologicals, S.A. (Belgium)
 19. **JANSSEN.** Janssen Pharmaceutica, N.V. (Belgium)
 20. **Novavax.** Novavax, Inc. (United States)
 21. **Pfizer.** Pfizer Limited (United Kingdom)
 22. **AZ.** AstraZeneca AB (Sweden)

- **Grant Agreement.** (including its annexes and any amendments) The agreement signed between the beneficiaries of the action and the IMI2 JU for the undertaking of the PROMISE project (Grant Agreement No. 101034339).
- **Project.** The sum of all activities carried out in the framework of the Grant Agreement.
- **Work plan.** Schedule of tasks, deliverables, efforts, dates, and responsibilities corresponding to the work to be carried out, as specified in Annex I to the Grant Agreement.
- **Consortium.** The PROMISE Consortium, comprising the above-mentioned participants.
- **Consortium Agreement.** The agreement concluded amongst PROMISE participants for the implementation of the Grant Agreement. The agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

Abbreviations

Acronym / Abbreviation	Meaning
UMC Utrecht	University Medical Center Utrecht
WP	Work Package
IRB	Institutional Review Board

Publishable summary

The protocol and additional documentation of the 2 clinical studies of Work Package (WP) 3 have been designed in close collaboration with WP2 and WP4 partners.

Study 1 is the PROMISE follow-up study and consists of extended follow-up of eligible infants of the RESCEU infant cohort study and the RESCEU infant case-control study with the aim to evaluate the incidence of asthma/wheeze at the age of 6 years in relation to RSV infection of different severity levels. An amendment for the original study protocol has been prepared for submission to the local Institutional Review Boards (IRBs).

Study 2 is the PROMISE case-control biomarker validation study. This study has the aims to validate the biomarkers found in the RESCEU infant studies and to validate a new severity score developed by WP1 and will be performed at UMC Utrecht. The protocol and additional documentation of this study have been approved by the UMC Utrecht IRB.

1. Introduction

Study 1 PROMISE follow-up study

The PROMISE follow-up study has the aim to evaluate asthma/wheeze at school age in relation to RSV infection of different severity levels. Parents of children of the RESCEU infant cohort and infant case-control study, who are already participating in the 2- and 3-year follow-up will be asked to continue follow-up until school age (age 6 years) with yearly questionnaires.

Study 2 PROMISE infant case-control validation study

In this validation study we will validate the biomarkers identified from the RESCEU infant case-control study. We will also validate a new severity score which is being developed by WP1. This study maintains a similar design to the RESCEU infant case-control study.

2. Methods

Study 1 PROMISE follow-up study

Parents of eligible children participating in the RESCEU infant cohort study and the infant case-control study will be asked informed consent to continue participating until age 6 years by means of yearly questionnaires at age 4, 5 and 6 years.

The following categories of children will be eligible for the follow-up study:

	Controls		RSV+			
	No ARTI hospitalization	Non-RSV hospitalization	Mild, no doctor's visit	Medical attention	Hospitalization	PICU
RESCEU: active birth cohort	829	2	70	91	7	1
RESCEU: passive birth cohort	9200	98	na	na	115	6
RESCEU: case-control study	na	na	na	80	150	53
Total	829	100	70	171	272	60
	Not available					
	Included in PROMISE		1500			
	Not in PROMISE		9200			

ARTI, acute respiratory tract infection; PICU, pediatric intensive care unit

Study 2 PROMISE infant case-control validation study

The case-control validation study will take place at UMC Utrecht (monocenter) and will provide biological samples for the PROMISE biobank (for analysis in WP3 and WP4) with the aim to validate biomarkers of severe disease and of sequelae in infants after RSV infection identified in the RESCEU case-control study. This study will also be used to validate a new severity score, which is being developed by WP1.

We will prospectively collect biological samples and clinical information from 160 previously healthy infants (<1 year of age) sub-divided into the following groups:

- Hospitalized, ventilated infants with RSV infection (N=40)
- Hospitalized, non-ventilated infants with RSV infection (N=40)
- Medically attended, non-hospitalized infants with RSV infection (N=40)
- Healthy infants without respiratory tract infection (N=40)

3. Results

Study 1 PROMISE follow-up study

The additional questionnaires at age 4, 5 and 6 years have been designed in close collaboration with RESCEU WP3 and is based on the RESCEU infant studies 2- and 3-year questionnaires to allow comparison at different ages. A protocol amendment has been drafted for the RESCEU infant cohort and infant case-control study. Each participating centre of the RESCEU infant studies has submitted this amendment to their local IRB for approval.

Local IRB reference numbers:

Site and RESCEU study	Local IRB	Reference number
TURKU infant cohort study	Varsinais-Suomen sairaanhoitopiirin kuntayhtymän eettiselle toimikunnalle	17201
UEDIN infant cohort study	South East Scotland Research Ethics Committee 01	IRAS project ID: 224486 REC: 17/SS/0086
SERGAS infant cohort study	Comité de Ética de la Investigación de Santiago-Lugo	2017/175
SERGAS infant case-control study	Comité de Ética de la Investigación de Santiago-Lugo	2017/395
UOXF infant cohort study	South Central -Oxford B Research Ethics Committee	IRAS project ID: 223673 REC: 17/SC/0335
UOXF infant case-control study	South Central and Hampshire A Research Ethics Committee	IRAS project ID: 231136 REC: 17/SC/0522
UMCU infant cohort study	Medical Ethical Committee, UMC Utrecht	NL60218.041.17 17/069
UMCU infant case-control study	Medical Ethical Committee, UMC Utrecht	NL62657.041.17 17/563

All sites expect to have IRB approval for this amendment by April 2022. Study documents are available on the PROMISE SharePoint site.

Study 2 PROMISE infant case-control validation study

The protocol and additional documentation of the infant case-control validation study have been prepared in close collaboration with WP4 partners and submitted to the UMC Utrecht Institutional Review Board (IRB) at an early stage to allow enough time for recruitment of eligible children and taking into account the changes in RSV seasonality due to the COVID-19 pandemic and non-pharmaceutical interventions.

The UMCU Utrecht IRB reviewed and approved the study on 16 September 2021 (IRB No. NL78337.041.21/ 21-486/D). Submitted documents (protocol, patient information sheet and consent form, case report forms, and questionnaires) are available on the PROMISE SharePoint site. The study protocol was submitted earlier as Deliverable 3.1.

4. Conclusion and next steps

Study 1 PROMISE follow-up study

The study documents, including the protocol amendment for the RESCEU infant studies, have been finalized. The amendment has been submitted to the local IRBs at participating centers. All sites expect to have IRB approval for this amendment by April 2022.

Study 2 PROMISE infant case-control validation study

The study documents, including the protocol, have been finalized. Full IRB approval has been obtained and recruitment of eligible infants started in November 2021. However, due to the changing seasonality of RSV because of the COVID-19 pandemic the number of eligible infants has been considerably less than expected, resulting in a lower number of recruited infants than expected for which a mitigation plan is being developed.

ANNEXES

ANNEX I. Protocol amendment study 1

AMENDMENT
RESCEU infant cohort study
and
RESCEU infant case-control study

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SUMMARY

Rationale: RSV infection causes a substantial burden in the first year of life. Although premature born infants and infants with cardiorespiratory comorbidity have a higher risk of severe RSV disease, the disease burden is also considerable in previously healthy infants, as is shown by the preliminary analysis of the RESCEU infant cohort study, indicating a hospitalization rate of more than 1%. It is known that RSV infection in the first year of life is associated with recurrent wheezing, which our preliminary results of the RESCEU infant cohort and infant case-control study confirm. It is still unclear whether RSV infection early in life is associated with the development of asthma at school age and what are the mechanisms of this possible association.

The RESCEU infant studies have built up 2 cohorts of a large number of well-defined and well described children with and without an RSV infection in the first year of life. Part of these children have already been followed up by yearly questionnaires until age 3. By extending the follow-up until school age (age 6 years) we expect to obtain important information about the association between RSV infection in the first year of life and the development of asthma.

Objective: To determine the relationship between infant RSV infection of different severity and school age asthma.

Study design: Observational follow-up study

Study population: All children participating in the RESCEU infant cohort study/infant case-control study who were eligible for 3 year follow-up.

Main study parameters/endpoints: The relationship between infant RSV infection of different severity and school age asthma. Incidence of asthma/wheeze at the age of 6 years will be compared between different severity levels of RSV infection in the first year of life and controls (children without symptomatic RSV infection).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: This amendment request is limited to additional yearly questionnaires. No extra clinical specimen will be collected. Therefore the burden and risks associated with participation in this amendment are considered negligible.

There is no clear clinical benefit for the subjects participating in this amendment. However, the results of this study aim to support the understanding of the relation between RSV disease and the development of asthma at school age, which is important for the implication of future preventive and therapeutic interventions.

1. INTRODUCTION AND RATIONALE

RSV infection causes substantial burden in the first year of life. Although premature born infants and infants with cardiorespiratory comorbidity have a higher risk of severe RSV disease, the disease burden is also considerable in previously healthy infants, as is shown by the preliminary analysis of the RESCEU infant cohort study, indicating a hospitalization rate of more than 1%. Given this significant burden of RSV in the first year of life, it is important to also look at long term sequelae of severe RSV infection to understand the long term consequences of RSV infection early in life. It is known that RSV infection in the first year of life is associated with recurrent wheezing (1), which our preliminary results of the RESCEU infant cohort and infant case-control study confirm. It is still unclear whether RSV infection early in life is associated with the development of asthma at school age (2, 3) and what are the mechanisms of this possible association (are infants with an atopic predisposition more prone for severe RSV infection or is RSV infection at a young age causing long term damage to the developing airways leading to asthma at school age). Moreover, studies were mainly performed in preterm infants and no large prospective cohort studies have reported about the association between RSV infection in infancy and asthma development in healthy term infants.

The RESCEU infant studies have built up 2 cohorts of a large number of well-defined and well described healthy term born children (n~10,000) with and without an RSV infection of different severity in the first year of life. Part of these children (n~1500) already have been followed up by yearly questionnaires until age 3. By extending the follow-up until school age (age 6) we expect to obtain important information about the association between RSV infection at an early age and the development of asthma.

2. OBJECTIVES

Primary Objective: To determine the relationship between infant RSV infection of different severity and school age asthma.

Secondary Objective(s):

1. To compare the incidence of asthma after RSV hospitalization with incidence of asthma after hospitalization because of other viral infections.
2. To determine risk factors for persistent wheeze at age 3 and 6 years.

3. STUDY DESIGN

For this follow-up study data about children participating in the RESCEU birth cohort study and the RESCEU case-control study will be combined in a case-control design. The RESCEU birth cohort study consists of healthy term born infants who were recruited at birth and followed during the first year of life to determine the incidence of RSV infection (active birth cohort, n=1,000) and RSV related hospitalization (active and passive birth cohort, n=10,000). The RESCEU case-control study is a biomarker study to determine biomarkers for severe RSV infection. Cases were determined as previously healthy infants hospitalized with RSV infection. Controls were determined as previously healthy infants with RSV infection who were not hospitalized.

RSV positive children of the RESCEU birth cohort study and RESCEU case-control study will be defined as cases and will be divided in 4 severity categories:

- Mild disease, no doctors visit
- Medically attended, no admission
- Hospitalized, no intensive care required
- Admitted to pediatric intensive care unit

Two RSV-negative control populations are recruited and will be defined as controls:

- Children participating in the active birth cohort who had no symptomatic RSV infection
- Children participating in the birth cohort study who were hospitalized for RSV-negative respiratory infection.

All these children are currently followed up by yearly questionnaires about amongst other doctors' visits because of respiratory symptoms, wheezing episodes and use of respiratory medication until the age of 3 years. In this amendment, parents of participating children will be asked to continue to fill out yearly questionnaires until the age of 6 years. These questionnaires will contain questions about asthma/wheezing episodes, use of asthma medication (inhalation medication) and doctors' visits for respiratory symptoms. If parents indicate that they have visited a doctor or have been admitted for respiratory symptoms, medical charts of the attended physician and/or hospital will be reviewed.

4. STUDY POPULATION

4.1 Inclusion criteria

Children participating in the RESCEU birth cohort study who:

- Participated in the active birth cohort study
- Participated in the passive birth cohort study and were hospitalized because of an ARTI

Children participating in the RESCEU case-control study group 1a and 1b:

- Group 1a: previously healthy infants who are hospitalized with RSV
- Group 1b: previously healthy infants who are RSV positive but are not hospitalized

4.2 Exclusion criteria

No informed consent for further follow-up after the age of 3.

5. METHODS

5.1 Study parameters/endpoints

5.1.1 Main study parameter/endpoint

The primary outcome is the relationship between infant RSV infection of different severity and school age asthma. Incidence of asthma/wheeze at the age of 6 years will be compared between different severity levels of RSV infection in the first year of life and controls (children without symptomatic RSV infection).

The following outcome measures will be used:

- Parent reported asthma symptoms (yearly questionnaires)
- Use of asthma medication (yearly questionnaires)
- Physician diagnosed asthma (medical charts review)

5.1.2 Secondary study parameters/endpoints

1. Incidence of asthma after RSV hospitalization compared to hospitalization because of other viral infections
2. Risk factors for persistent wheeze at age 3 and 6 years

5.2 Study procedures

Participants will be followed-up by means of yearly parental questionnaires around their 4th, 5th and 6th birthday. These online/paper/phone questionnaires will be similar to the questionnaires at age 1, 2 and 3 and contain questions about amongst other doctors' visits and hospitalizations because of respiratory symptoms, asthma/wheezing episodes and use of asthma medication (inhalation medication). In

addition, data about costs, resource use and HRQoL will be asked. If parents indicate that they have visited a doctor or have been admitted because of respiratory symptoms, medical charts of the attended physician and/or hospital will be reviewed.

6. STATISTICAL ANALYSIS

6.1 Primary study parameter(s)

The primary outcome is the relationship between infant RSV infection of different severity and school age asthma. Incidence of asthma/wheeze at the age of 6 years will be compared between different severity levels of RSV infection in the first year of life and controls (children without symptomatic RSV infection). Potential confounders, including known asthma risk factors will be added as covariates. Asthma outcomes will be related to variables during the first year of life, including known asthma risk factors, RSV status, RSV-related biomarkers as well as the respiratory microbiome at birth.

6.2 Secondary study parameter(s)

1. Difference in incidence of asthma between RSV hospitalization and hospitalization because of other viral infections.

Incidence of asthma at school age will be compared between children who were admitted to the hospital with RSV in their first year of life and children who were admitted with other viral respiratory tract infections. If possible, the difference in incidence per virus (group) will be calculated.

2. Risk factors for persistent wheeze at age 3 and 6 years.

Risk factors for persistent wheeze will be determined using demographic parameters, clinical parameters and outcome of participating infants. Multivariate regression analysis will be performed to analyse multiple risk factors for persistent wheeze.

ETHICAL CONSIDERATIONS

6.3 Recruitment and consent

Parents/caregivers of children participating in the study who were eligible for the 2 and 3 year follow-up will be asked informed consent for additional follow-up by means of yearly questionnaires. An email/letter will be sent after the 3rd birthday to ask whether the parents are willing to continue with yearly questionnaires until age 6. If they agree they are asked to sign the informed consent form and send it back. If parents have additional questions or if they do not respond, they will be called by the study team to explain the follow-up study, to answer any questions and to ask whether they are willing to participate.

6.4 Benefits and risks assessment, group relatedness

This amendment only relates to additional yearly questionnaires. No extra clinical specimen will be collected. Therefore the burden and risks associated with participation in this amendment are considered negligible.

There is no clear clinical benefit for the subjects participating in this amendment. However, the results of this study aim to support the understanding of the relation between RSV disease and the development of asthma at school age, which is important for the implication of future preventive and therapeutic interventions.

7. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

7.1 Handling and storage of data and documents

For this follow-up study a new database will be built in Castor EDC. Castor EDC is a GCP and GDPR compliant electronic data capture (EDC) system with the same level of security and data protection as Research Online/Redcap. Castor EDC is user-friendly, allowing researchers to develop a database themselves and is supported by the UMC Utrecht data management team.

Castor is a web-based EDC system; data that is submitted will be stored in cloud based databases. Databases and web servers are hosted in data centers that meet the highest possible security requirements.

Castor EDC will only capture data without subject identifiable data. Only unique study identifiers will be used to identify the subjects in the eCRF database. The database will be checked by the UMC Utrecht data management team before data are entered. Local teams will log subject identifiable data (for example, name, contact data and date of birth) in a separate document to link the subject to the correct ID number noted on the eCRF. This document will only be accessible for local researchers and will be stored locally in a secure, password protected file and/or locked cabinet. In this way there will be no direct link between personal data and clinical research data.

Castor EDC fulfils all legal and privacy requirements (amongst others GDPR and European legislation). This means, among other things, that users will get role-based access to the system after they have logged-in using their own username and password. The role-based access to the system will avoid unauthorised data access and will prevent users from performing actions that they are not authorised to perform. Furthermore, the system will log all data entry steps with timestamps, update reasons and user information and are designed in such a way that data changes are documented and that there is no deletion of entered data.

8. REFERENCES

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