RESEARCH PROTOCOL

REspiratory Syncytial virus Consortium in EUrope (RESCEU) study: Defining the burden of disease of Respiratory Syncytial Virus in older adults in Europe.

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LIST OF ABBREVIATIONS (FOR RELEVANT DEFINITIONS, SEE APPENDIX 2)

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
AE	Adverse Event
AR	Adverse Reaction
ARTI	Acute Respiratory Tract Infection
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
COPD	Chronic Obstructive Pulmonary Disease
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EDC system	Electronic Data Capture system
EU	European Union
GCP	Good Clinical Practice
GP	General Practitioner
HRQoL	Health related Quality of life
IC	Informed Consent
MA	Medically Attended
METC	Medical Research Ethics Committee (MREC); in Dutch: Medisch Ethische Toetsing Commissie (METC)
NA	Not applicable
POC test	Point of Care test
QoL	Quality of Life
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
(S)AE	(Serious) Adverse Event
SD	Standard deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)

SUMMARY

Rationale: The REspiratory Syncytial virus Consortium in EUrope (RESCEU) is an Innovative Medicine Initiative (IMI) funded by the EU and EFPIA under the H2020 framework to define and understand the burden of disease caused by human respiratory syncytial virus (RSV) infection. RSV causes severe disease in individuals at the extremes of the age spectrum and in high risk groups. It was estimated that RSV was associated with 34 million cases of acute respiratory tract infection (ARTI), 3.4 million ARTI hospitalizations and 55,000 to 199,000 deaths in children <5 years in 2005 worldwide. The estimated burden of disease in older adults is comparable with non-pandemic influenza A (for which a vaccine is available). These estimates were based on limited data and there is a substantial gap in knowledge on morbidity and associated healthcare and social costs in Europe. New vaccines and therapeutics against RSV are in development and could soon be available on the European market. RESCEU will deliver knowledge of the incidence and burden of RSV disease in young children and older adults in Europe, which is essential for stakeholders (governments, etc.) to take decisions about prophylaxis and treatment.

Objective: To determine the burden of disease due to RSV in older adults.

Study design: Prospective epidemiological, observational, multi-country, multicenter cohort study.

Study population: Adults aged 60 years and up (n= approximately 1,000).

Main study parameters/endpoints:
The primary endpoints of the study are;

- RSV associated medically attended (MA) ARTI.
- RSV related hospitalization.
- The incidence of RSV infection-associated ARTI.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:
A blood sample (60 ml) and a nasopharyngeal swab will be collected at the beginning (August/September) and end (May/June) of the RSV season. The drawing of blood can be moderately painful. The collection of a nasopharyngeal swab can cause a brief moment of discomfort. Participants will be asked weekly by telephone (verbal or text message), email or telephone app about any signs of respiratory tract infections. In the event of an ARTI two nasopharyngeal and one oropharyngeal swab will be collected to perform a direct reverse transcriptase polymerase chain reaction (RT-PCR) for RSV and additional analyses if RT-PCR is positive for RSV. If a participant experiences a RSV positive ARTI, blood will be drawn (60 ml) and a nasopharyngeal swab will be collected at the time of the infection and 1-2 weeks after onset of symptoms. During the course of each ARTI, independent of RSV status, participants will be asked to complete a short daily diary in order to score respiratory symptoms and quality of life. At inclusion and after approximately one year (+/- 2 months, at least after the RSV season) participants are asked to fill in a short questionnaire.

None of the RESCEU study procedures is associated with any risk for serious complications. However, there is a minimal risk of minor complications due to study procedures (for example a nose bleed after a nasopharyngeal swab or bruise after a blood test).

Possible benefit: There is no clear clinical benefit for the participants taking part in this proposed study. However, the results of this study aim to support the understanding of the burden of RSV disease, which is important for the implication of future preventive and therapeutic interventions.

1. INTRODUCTION AND RATIONALE

The RESCEU clinical cohort studies - summary

The IMI-funded REspiratory Syncytial virus Consortium in EUrope (RESCEU) programme includes an observational study to define the burden of disease caused by human respiratory syncytial virus (RSV) infection. A total of 4 clinical studies in specific risk groups will be performed in several European countries as part of the RESCEU study. The sites of these studies were selected because of their experience in acute respiratory tract infection (ARTI) and/or RSV research in specific risk groups.

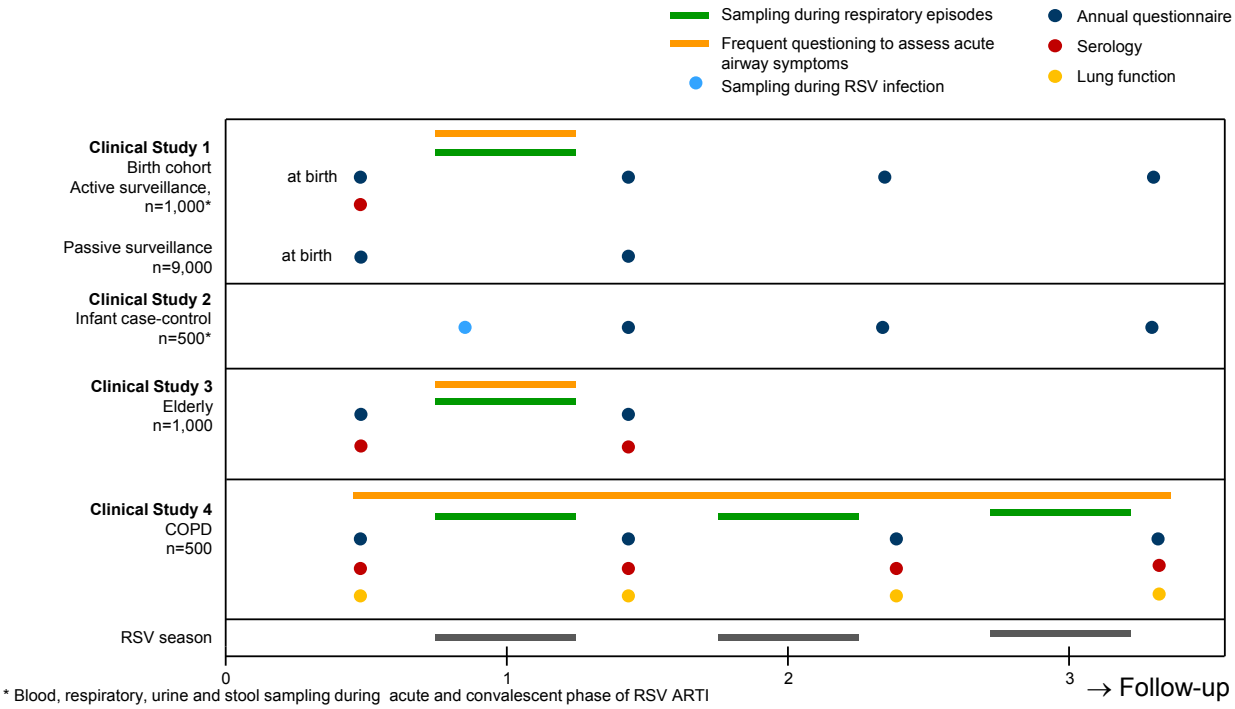
The clinical cohort studies in young children (clinical study 1 and 2, fig. 1) will be conducted at the UMC Utrecht (Netherlands), University of Turku (Finland), Servicio Galego de Saúde (Spain), University of Oxford, University of Edinburg and Imperial College London (United Kingdom).

The clinical cohort study in older adults (elderly) (clinical study 3, fig.1) will be conducted at the UMC Utrecht (Netherlands), University of Antwerp (Belgium) and University of Oxford (United Kingdom).

The clinical cohort study in chronic obstructive pulmonary disease (COPD) patients (clinical study 4, fig. 1) will be conducted at the UMC Groningen (Netherlands) and Imperial College London (United Kingdom).

This protocol is restricted to Clinical Study 3.

Figure 1. Overview of clinical studies embedded in the RESCEU effort and follow up periods for included (individual) patients.



Background

Human respiratory syncytial virus (RSV) causes severe disease in individuals at the extremes of the age spectrum and in high risk groups. It was estimated that RSV was associated with 34 million cases of acute respiratory tract infection (ARTI), 3.4 million ARTI hospitalizations and 55,000 to 199,000 deaths in children <5 years in 2005 worldwide.[1] These estimates were based on limited data and there is a substantial gap in knowledge on morbidity and associated healthcare and social costs in Europe. RSV infection in childhood is associated with subsequent wheezing and asthma.[2-4] These long-term sequelae pose a substantial additional burden on the healthcare system. In addition, RSV is a significant cause of ARTI morbidity in elderly and COPD patients.[5,6] Most published data on RSV disease burden in the elderly (aged >65 years) are from the United States and from hospital settings and describe a disease burden similar to non-pandemic influenza A.[5]

Treatment and prophylaxis options are limited. Mostly only supportive care is available for patients with severe RSV ARTI. Ribavirin has been used as treatment, but with limited evidence of benefit and is therefore not routinely recommended. Various new RSV vaccines and therapeutics could be available in the near future.[7] To use these new vaccines and therapeutics in the best possible way and to guide their development and implementation, it is necessary to determine the burden of RSV disease in Europe to gain better insight in disease severity in young children and older adults and the associated societal and healthcare costs.

There is a parallel need to assemble clinical resources to identify the correlates of severe RSV disease for clinical management, classification of disease severity in clinical trials and identification of biomarkers for severe disease, which are currently lacking.[8]

For this purpose RESCEU (REspiratory Syncytial virus Consortium in EUrope) has been set up. RESCEU will perform the first prospective multi-center study in both older adults and children to provide accurate data on RSV disease incidence and sequelae (long-term airway morbidity, including asthma) and economic consequences of RSV infection.

The following document will describe only the protocol for the adult cohort study. The other prospective cohort studies are presented in separate protocols for these specific cohorts.

We will prospectively follow-up a cohort of approximately 1,000 older adults (≥60 years, of whom approximately 500 will be ≥75 years) living in the community during one year to obtain incidence data on RSV infection, medically attended (MA) RSV infection and hospitalization due to RSV.

2. OBJECTIVES

Table 1. Primary and secondary objectives and associated endpoints.

	Objectives	**Endpoints**
Primary	• To estimate the incidence of RSV MA-ARTI in both inpatients and outpatients and overall RSV infection-associated ARTI in older adults.	• Incidence rate of RT-PCR confirmed RSV infection-associated MA-ARTI in inpatients outpatients and overall RT-PCR confirmed RSV in older adults. Data collected by using samples, medical data from the hospital and questionnaires.
Secondary	• To estimate the rate of all-cause MA (inpatient or outpatient) ARTI and related medical complications (exacerbations of chronic conditions, acute cardiovascular events).	• Incidence rate of all-cause MA ARTI or events leading to worsening of cardiorespiratory status. Data collected by using diary, questionnaires.
	• To estimate the RSV-associated and all-cause mortality.	• Mortality through the RSV season of follow up for RSV-associated deaths and all cause deaths. Data collected by using medical data from the hospital and questionnaires.
	• To estimate health care costs, health care resource use, interruption of normal activities, and HRQoL in RSV-associated and all-cause MA (inpatient or outpatient) ARTI patients.	• Health care costs and resource use, interruption of normal activities, and HRQoL in RSV-associated and all-cause MA (inpatient or outpatient) ARTI patients. Data collected by using diary, questionnaires.
	• To estimate the incidence of RSV-related secondary bacterial pneumonia events and their association with antibiotic use within 21 days after onset of RSV infection.	• Incidence rate of RSV-associated secondary bacterial pneumonia events (defined as pneumonia within 21 days after RSV infection) and associated antibiotic use. Data collected by using medical data from the hospital, diary and questionnaires.
	• To collect clinical samples for biomarker analysis on possible biomarkers which are predictive of	• Sample collection for biomarker analysis. Establish a Biobank for identifying potential biomarkers of

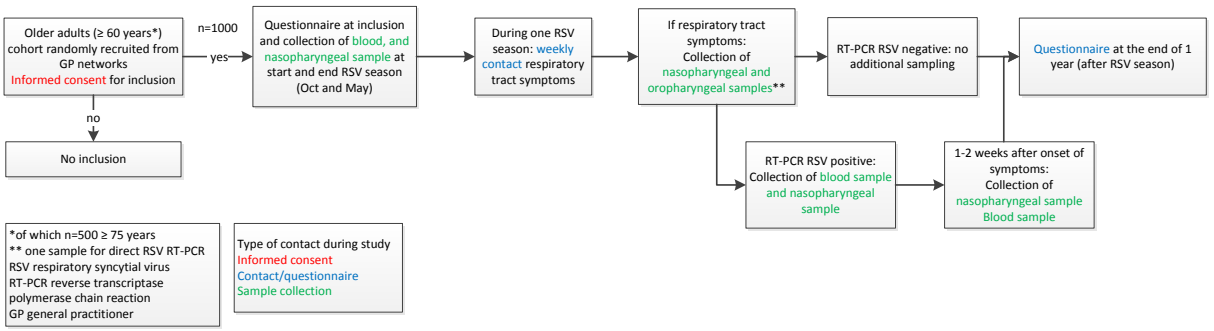
	severe or complicated RSV disease in older adults. With these clinical samples a biobank will be established for identifying potential biomarkers of RSV disease severity for further validation.	RSV disease severity for further validation.
	• To examine the incidence of other respiratory pathogens associated with all MA-ARTI	• Incidence rate of other respiratory pathogens associated with all MA-ARTI. Data collected by using samples.
	• To estimate the proportion of viral ARTI attributable to RSV.	• Proportion of viral ARTI attributable to RSV. Data collected by using samples.
	• To estimate important risk factors for RSV infections (by severity and healthcare utilizations).	• Important risk factors of RSV infection. Data collected by using baseline questionnaires.
	• To determine change in frailty over the course of the study	• Change in frailty over the course of the study. Data collected by using diary, questionnaires.

3. STUDY DESIGN

This will be a multi-country, multicenter, prospective, observational cohort study conducted across 2 consecutive winter seasons to determine the incidence of RSV infection, RSV associated MA-ARTI and RSV related hospitalization in participants ≥60 years of age, recruited from the general population.

These older adults will be recruited from general practitioner (GP) networks between May and October of each year for 2 consecutive years based on pre-specified selection criteria (see section 4.2 and 4.3). Practice lists will be screened for potentially eligible participants. They will be informed by their GP about the study. If they consent that their contact details can be given to the study team, interested potential participants will be contacted by a member of the study team who will answer any questions they may have about the study.
When participants are willing to be enrolled in the study, an inclusion visit is booked at the beginning of the RSV season (August/September). During the same visit a blood sample and a nasopharyngeal sample will be collected and a baseline questionnaire about demographic data, medical history, smoking habits and quality of life will be completed.
During the RSV season (October 1st to May 1st, or longer if RSV is still circulating, based on country specific surveillance reports), respiratory tract symptoms will be assessed weekly by telephone contact (verbal or text message), email, (daily) telephone app or online questionnaire. If the participant experiences an ARTI, the study team will visit the participant to collect two nasopharyngeal and one oropharyngeal sample for direct RSV RT-PCR and additional analyses. If RSV is positive a blood sample and nasopharyngeal sample will be obtained at the time of infection and an additional blood and nasopharyngeal sample will be collected 1-2 weeks after the onset of symptoms. At the end of the RSV season (May/June) another blood and nasopharyngeal sample will be collected. Individual participants will be followed up for one RSV season. After approximately one year (+/-2 months) participants will be asked to fill in a questionnaire to finalize follow-up. This questionnaire is about, but not limited to, respiratory disease in the past year, changes in living conditions, health status, frailty and quality of life.
An overview of the study design and main procedures is given below (Figure 2).

Figure 2. Overview of study design and main procedures of cohort of older adults.



4. STUDY POPULATION

4.1 Population (base)

Cohort of approximately 1,000 older adults (≥60 years, including approximately 500 ≥75 years). Participants will be randomly recruited from the database of general practitioners in the following countries: the Netherlands (UMCU), Belgium (UA) and United Kingdom (UOXF).

4.2 Inclusion criteria for enrolment

All participants must satisfy ALL the following criteria at study entry:

- Male and female adults ≥60 years of age (comorbidity, including chronic heart disease is not an exclusion criterion)
- Willing and able to give written informed consent
- Willing and able to adhere to protocol-specified procedures

4.3 Exclusion criteria for enrolment

The following criteria should be checked at the time of study entry. If ANY exclusion criterion applies, the subject must not be included in the study:

- Current alcohol or drug abuse or history of unsuccessfully treated alcohol or drug abuse within the past year
- Unable to perform the study procedures
- Dementia
- Life expectancy less than 1 year
- Any known or suspected immunosuppressive condition, acquired or congenital, as determined by history and/or physical examination (a more detailed description/list can be found in appendix 3).
- Chronic administration (defined as more than 14 continuous days) of immunosuppressants or other immune-modifying drugs within 6 months prior to study participation. The use of topical, inhaled, and nasal glucocorticoids will be permitted (a more detailed description/list can be found in appendix 3).
- Previous participation in this study or in a RSV interventional trial (vaccine, antivirals).
- Planned leave/holiday during the winter season of more than 1 month in total.

4.4 Sample size calculation

For the primary analysis the ratio between cases of RSV-related hospitalizations and number of older adults in the total population will be calculated. In addition, the ratio between the cases of MA-RSV infection and the number of older adults undergoing active surveillance will be calculated.

To estimate the incidence of MA-RSV infection and RSV-related hospitalization at an older age, a prospective cohort of approximately 1,000 older adults ≥60 is followed for 1 year. For sample size calculations a statistic expert of the Julius Support Center was consulted. Assuming a yearly MA-RSV incidence of 3,0% based on literature[5,9], a sample size of 800 will produce a two-sided >95% confidence interval with a symmetric half width of 0.01

(Confidence interval formula: Exact, Clopper-Pearson). Accounting for a 10% loss to follow up, approximately 1000 elderly will be included in the cohort.

Patient population	Sites	Outcome	Persons	RSV seasons	Expected Incidence per year (%)	95% Confidence Interval Half-Width (%)
Older Adults (≥ 60 years)	NL, UK, BE	Incidence rate of MA-RSV	1,000	1	3,0 [5,9]	1,9 – 5,0

5. METHODS

5.1 Study parameters/endpoints (see also Table 1)

5.1.1 Main study parameter/endpoint

The primary endpoint is the incidence rate of RT-PCR confirmed medically attended RSV infection-associated ARTI in both inpatients and outpatients as well as the incidence of RSV in the overall study population of older patients. The incidence rate will also be summarized separately for outpatient events and for both inpatient and outpatient events combined through the RSV season of follow up. Nasopharyngeal and oropharyngeal swabs collected during ARTI episodes during the RSV season will be used for reverse transcriptase polymerase chain reaction (RT-PCR) detection of RSV. Pre- and post RSV-season RSV serology will be performed in order to capture RSV infected individuals which will be missed by active surveillance. In order to analyze the microbiome and transcriptome a nasopharyngeal and oropharyngeal swab will be collected pre- and post RSV-season.

5.1.2 Secondary study parameters/endpoints

1. The incidence rate of all-cause MA-ARTI or events leading to worsening of cardiorespiratory status. The incidence rate will also be summarized separately for outpatient events and for both inpatient and outpatient events combined through the RSV season of follow up. Subgroup analyses will summarize these endpoints by RSV season.
2. Mortality through the RSV season of follow up for RSV-associated deaths and all cause deaths.
3. Health care costs and resource use for RSV-associated and all-cause MA-ARTI (inpatient or outpatient) or events leading to worsening cardiorespiratory status with regard to hospital duration, incidence and duration of intensive care unit stay, supplemental oxygen use, antibiotic and antiviral use and number of outpatient visits (e.g., ER visit, physician office/outpatient visits) and HRQoL.
4. The incidence rate of RSV-associated secondary bacterial pneumonia events (defined as pneumonia within 21 days after RSV infection) and associated antibiotic use will be summarized.
5. Change in frailty over the course of study.
6. Sample collection for biomarker analysis to investigate possible biomarkers which are predictive of severe or complicated RSV disease in older adults. With these

clinical samples a biobank will be established for identifying potential biomarkers of RSV disease severity for further validation.

5.2 Randomisation, blinding and treatment allocation

There is no randomisation, blinding or treatment allocation, because no investigational product is being administered in this study.

5.3 Study procedures

1. Inclusion Visit (August/September)
At the inclusion visit, after eligibility has been confirmed and fully informed consent completed, the following procedures will take place:

- A baseline questionnaire about, but not limited to, demographic data, medical history, risk factors for RSV disease and quality of life will be completed.
- A blood sample (60 ml) and a nasopharyngeal sample will be collected.

2. Throughout the RSV season (October 1st to May 1st, or longer if RSV is still circulating based on national viral surveillance programs):
Participants will be asked about respiratory symptoms during the RSV winter season by weekly contact by telephone (verbally or text message), email, telephone app or online questionnaire. If they experience an ARTI, participants are instructed to contact the study team. Two nasopharyngeal and one oropharyngeal sample will be collected by home visits (or in the doctor's office when preferred by participant) within 3 days after contact with the study team. One nasopharyngeal sample will be used for direct RSV RT-PCR testing. The other samples will be stored at -80°C. If RSV is positive a blood sample will be drawn (60 ml) and a nasopharyngeal sample will be collected and stored at -80°C. In addition, in case of a RSV ARTI, 1-2 weeks after onset of symptoms another blood sample (30ml) and nasopharyngeal sample will be collected. During the episode of respiratory disease, participants are asked to complete a diary on respiratory symptoms and HRQoL. At the end of the episode, participants are asked to complete a questionnaire on medical resource use, interruption of daily activities and HRQoL. If participants have been admitted to the hospital, a questionnaire about the reason for hospitalization, diagnosis and treatment will be completed by the study team using medical data from the admitted hospital.

3. At the end of the RSV Season (May/June)

- A blood sample (60 ml) and a nasopharyngeal sample will be collected.

4. Approximately one year after inclusion (+/- 2 months).

- A questionnaire about changes in living conditions, health status and quality of life will be completed.

Table 2. Overview of sampling of older adults study.

Moment of sampling	**Sample**	**Volume**	**Analysis (minimum amount)**
At beginning of RSV season (Oct.)	Serum (venous)	20 ml	RSV serology (350-400 µl) Proteome (100 µl)*
	Paxgene (venous)	10 ml	Transcriptome (200 µl)*
	Whole blood (venous)	30 ml	DNA/GWAS (200 µl) Epigenetics* Cellular immunology#
	Nasopharyngeal swab	n/a	Airway microbiome Airway transcriptome*
ARTI	Nasopharyngeal swab (2x) and oropharyngeal swab	n/a	RSV RT-PCR (qualitative) Multiplex RT-PCR respiratory viruses (quantitative) (pending funding) (RSV viral (deep) sequence analysis)
RSV ARTI	Serum (venous)	20 ml	RSV serology (350-400 µl) Proteome (100 µl)*
	Paxgene (venous)	10 ml	Transcriptome (200 µl)*
	Whole blood (venous)	30 ml	Epigenetics* Cellular immunology#
	Nasopharyngeal swab	n/a	Airway microbiome Airway transcriptome*
1-2 weeks after RSV ARTI	Nasopharyngeal swab	n/a	Airway microbiome*
	Whole blood (venous)	30 ml	Cellular immunology#
At end of RSV season (May)	Serum (venous)	20 ml	RSV serology (350-400 µl) Proteome (100 µl)*
	Paxgene (venous)	10 ml	Transcriptome*
	Whole blood (venous)	30 ml	Epigenetics*
	Nasopharyngeal swab		Airway microbiome Airway transcriptome*

* and additional RSV related biomarkers

in subset of subjects

Handling and storage of samples

All samples will be stored at the site where they are collected (medical center or local laboratory):

- Blood samples will be collected in appropriate tubes as described in table 2 and will be stored at -80°C for later analysis.
- Nasopharyngeal swab: a nasopharyngeal swab will be collected and aliquoted directly in 3-4 samples of 200 microliter. All aliquots will be stored at -80°C for later analysis
- Oropharyngeal swab: an oropharyngeal swab will be collected and stored at -80°C for later analysis.

5.4 Withdrawal of individual participants

Participants can withdraw from the study at any time without having to provide a reason if they wish to do so and without any consequences for their health care. The investigator can also decide to withdraw a subject from the study if they meet the pre-defined exclusion criteria (see section 4.3).

Withdrawal of consent: If consent is withdrawn, the participant will not have any further study procedures or study observations. All previously collected samples and data will be retained and used as planned, unless consent is specifically withdrawn for this.

Lost to follow-up: Participants will be considered lost-to-follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the subject's RSV status at approximately 1 year.

5.5 Replacement of individual participants after withdrawal

After withdrawal of an individual participant he or she will be replaced depending on the moment of withdrawal.

5.6 Premature termination of the study

Not applicable.

6. SAFETY REPORTING

6.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the participants and the reviewing research ethics committee if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by

the research ethics committee, except insofar as suspension would jeopardise the participants' health. The investigator will take care that all participants are kept informed.

6.1.1 Adverse events (AEs) and Serious adverse events (SAEs)

SAEs directly related to one of the interventions (venepuncture, nasopharyngeal or oropharyngeal swab) will be registered. Only these SAEs will be registered, as this is a non-interventional, low risk, observational study. AEs directly related to one of the interventions (for example a nose bleed after a nose swab or bruise after a blood test) will not be registered.

6.1.2 Suspected unexpected serious adverse reactions (SUSAR)

NA

6.1.3 Annual safety report

NA

6.2 Follow-up of adverse events

All AEs and SAEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.
The investigator will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the investigator has first knowledge of the serious adverse events. As mentioned in section 6.1.1, only SAE directly related to one of the interventions will be registered.

6.3 Data Safety Monitoring Board (DSMB)

No Data Safety Monitoring Board is needed. However, there will be 3 Advisory Boards, which will act as consultative bodies for ethical, scientific and technical matters.
The following advisory boards will be formed by external experts:

- International Scientific Advisory Group (ISAG)
- RESCEU Ethics Advisory Committee (EAC)
- RESCEU Patient Advisory Board (PAB).

See also appendix 1 for a detailed description of the governance structure of RESCEU.

7. STATISTICAL ANALYSIS

Descriptive statistics will be used to describe the incidence rate of hospitalization for RSV and MA-RSV infection in the cohort of older adults. Demographic parameters, clinical parameters and outcome and laboratory test results will be displayed as categorical data with percentages or continuous variables with mean (+/-SD) and/or median (interquartile range).

Comparisons between groups will be performed using chi-square for categorical variables, Student-t-test for normally distributed continuous variables or Mann-Whitney U test for not normally distributed continuous variables. Multivariate regression analysis will be performed to analyse multiple risk factors for RSV disease.
Statistical analyses will be performed using SPSS version 20 or a more recent version or with R statistical software version 3.0.1 or higher.

8. ETHICAL CONSIDERATIONS

8.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (www.wma.net) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

The recruiter will explain the nature of the study and will inform the participant that participation is voluntary and that the participant can withdraw from the study at any time. Written informed consent will be obtained from each participant prior to any study procedure. A copy of the signed consent form will be given to every participant and the original will be maintained by the research team.

8.2 Recruitment and consent

General practice patient lists will be screened for potentially eligible participants (see section 4.2 and 4.3). The latter will be informed by their GP about the study. If they are interested in taking part their contact details will be given to the study team. Interested potential participants will be contacted by a member of the study team who will answer any questions they may have about the study and if they are still interested booked in for an inclusion visit. Recruitment procedures can be adapted to local circumstances and regulations.
Participants that report a pneumonia during the study, or have missing data concerning a medically-attended ARTI, are asked additional informed consent to perform a medical notes review. This notes review includes amongst others obtaining report of physical examination, performed scans (chest X-ray), blood testing (CRP/ESR), prescription of medication (such as antibiotics or respiratory medication) and clinical diagnoses made by the physician. A medical notes review will be performed only in these specific cases in order to obtain or validate this information which is key for the primary and secondary study outcomes.

8.3 Benefits and risks assessment, group relatedness

- Nasopharyngeal swab: A small swab will be introduced deep into the nose and some mucus will be collected. The procedure can cause a brief moment of discomfort, however, the duration of this procedure is less than 10 seconds and the swab is very soft. Trained personnel will perform this. Minor complications (for example nose bleed) have been described, but are rare.

- Oropharyngeal swab: A small swab will be introduced into the mouth towards the oropharynx and some mucus of the oropharynx will be collected. This is a non-invasive technique. The procedure can cause a brief moment of discomfort, however, the duration of this procedure is less than 10 seconds and the swab is very soft. Trained personnel will perform this.
- Venipuncture: Drawing venous blood is moderately painful. Trained personnel will perform this. Minor complications like bruising have been described.

There is no clear clinical benefit for the participants taking part in this proposed study. However, the results of this study aim to support the understanding of the burden of RSV disease, which is important for the implication of future preventive and therapeutic interventions.

8.4 Compensation for injury

Due to the type of study, observational with non-invasive diagnostic procedures without major complications, as previously described, no serious adverse events are to be expected and participating in the study is with minimal risks. Therefore we request dispensation from the statutory obligation to provide insurance.

9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

9.1 Handling and storage of data and documents

Full data management will be performed by Julius Center. Data will be stored in a cloud-based database. Data will be anonymized before they enter the database. Each participant will receive a unique identification number, which cannot directly be traced back to the participant. The study team will keep a participant identification code list to trace data to an individual participant, if necessary. Data will be kept for at least 15 years. The handling of personal data will be in compliance to local regulations.

Data management of this study will be performed by a professional and experienced data management team. This team will coordinate and implement a high quality IT-infrastructure that will be necessary for the collection, controlling and reporting of the research data of this study.

A GCP compliant electronic data capture (EDC) system will be used to guarantee a correct, complete and consistent data collection. Web-based case report forms will be developed and implemented on the EDC system. By using comprehensive data validation checks within these forms, only data of high quality can be submitted to the study database. The forms, integrated into the EDC system, can easily be accessed by a standard web browser.

The data management system facilitates the collection of data, supports the monitoring processes and provides real time progress reports for management of the study. After last patient out, the database can rapidly be closed and data made available for further analysis and publication purposes.

The system meets all GCP guidelines for electronic data collection in terms of protecting data integrity and securing the information collected. This means, among other things, that users will get a role based access to the system after they have logged-in using their own username and password. The system will log all data entry steps with timestamps, update reasons and user information. The role based access to the system will avoid unauthorised data access and prevents that users perform actions that they are not allowed to do. Data from the EDC system will be transferred over the internet using secured data communication protocols. Data will be stored automatically and regularly back-ups will make sure that data never will be lost. Databases and web servers will be hosted in data centers that meet the highest possible security requirements.

9.2 Monitoring and Quality Assurance

Monitoring of the conduct of the study will be performed according to GCP guidelines at initiation and once yearly for the duration of the study. Monitoring is explained in more detail in the site specific separate monitoring plan.

9.3 Amendments

Amendments are changes made to the research protocol after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion. All substantial amendments will be notified to the METC. Non-substantial amendments will not be notified to the accredited METC, but will be recorded and filed by the sponsor.

9.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events, other problems, and amendments.

9.5 Temporary halt and prematurely end of study report

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.
Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

9.6 End of the study

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the moment that the last included participant has been followed up for 12 months.

9.7 Public disclosure and publication policy

Results of this research are disclosed unreservedly.

10. REFERENCES

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10. APPENDIX 1: Governance structure of RESCEU

RESCEU will adopt a governance model that will promote the active participation of national public health agencies, academia and pharmaceutical companies (EFPIA) in order to achieve maximum collaboration and data sharing. The management structure of RESCEU has been developed to respond to the needs of an international large-scale multi-stakeholder project. It is based on a traditional management structure adapted to the particular attributes of RESCEU.

Managing an organisation like RESCEU can be challenging due to the size of the project, its ambition, the variety of activities and their interdependencies. The project aims to harmonise the interests of the public and EFPIA partners. Therefore, a strong internal trust and communication interface is crucial to setting the project up for success.

The project is composed of complementary, as well as parallel activities, with strong inter-dependencies between critical work packages outputs. This will require the need for a detailed time schedule for many of the tasks, which will need close monitoring and communication between team members to avoid bottlenecks and to allow effective progress of deliverables.

The management structure needs to be a balance between a simplistic standard scheme (which will not be able to address the needs of a project of this level of complexity) and an excessive super-structure (that would impose a cumbersome bureaucracy to the project and thus impede its scientific and technical progress).

Taking into account these project characteristics, the management structure proposed for RESCEU is based on a multi-level organisation that balances:

- The fulfilment of the work plan *per se.*
- The management of trade-offs affecting scope, quality, time and cost.
- The primary focus needed on critical activities that aim to ensure the achievement of milestones and that contribute to strategic objectives.
- The relationships and trust amongst partners, including conflict resolution.
- The quality and efficiency with which the project activities are carried out.
- The appropriate implementation of the Consortium Agreement, with careful attention to the governance procedures, intellectual property policy and the related use of results.
- The implementation of the Grant Agreement, including administrative and financial elements.
- The creation and management of a wider scientific forum encompassing interested organisations beyond the project partnership (Associate Partners).

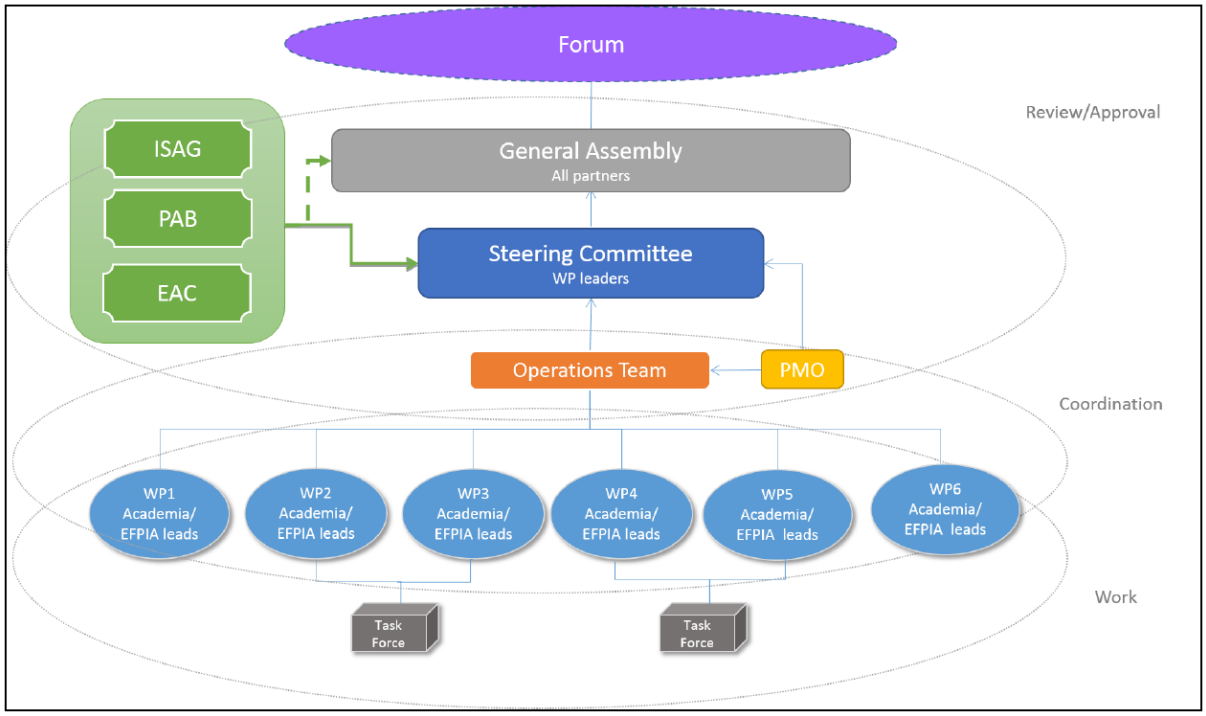
Taking into account the above, a management structure has been designed with the following components included:

- **RESCEU Forum (RF)**: forum for discussion, dissemination and scientific community-building within the project. The RF will consist of the project partners (Beneficiaries)

and the Associate Partners and may be convened by electronic means or face-to-face with the purpose of stimulating discussion and promoting dialogue on scientific issues. The RF will not have decision-making powers.

- **General Assembly (GA)**: body composed of all Beneficiaries participating in the project, with the ultimate decision-making responsibility in matters affecting the overall project strategy and composition of the consortium. The GA will meet annually and will adopt decisions by majority – each partner having a vote-, except in cases were unanimity is required according to IMI rules.
- **Steering Committee (SC)**: leadership team with 50/50 vote allocation between EFPIA/non-EFPIA members, composed of WP (Co-) Leads (from academia and EFPIA) or their designated representatives. The SC is responsible for decision making on most issues related to project execution, technical development decisions, work plan updates, and effort/budget re-assignment in order to pursue optimal efficiency. Meetings will take place regularly, typically every two months. The attendance of one representative from each WP will be required for quorum. Decisions will be determined by majority vote of attendees.
- **Operations Team (OT)**: executive group composed of the Coordinator, the Project Leader and the Project Manager (but not restricted to those), responsible for the day-to-day operational and technical aspects of the project. The OT will meet frequently (i.e. bi-weekly by teleconference) to monitor the project progress and to address any issues that may arise.
- **Project Management Office (PMO)**: team dealing with the day-to-day management of the project. Regular meetings, mostly by teleconference, will be established to appropriately follow up on management matters.
- **Task Forces**: Result-oriented ad-hoc teams will be created as needed, with a clear and exclusive mission of studying/resolving any issues between WPs.
- **Advisory Boards:** consultative bodies for ethical, scientific and technical matters. RESCEU intends to establish three advisory boards formed by external experts: the **International Scientific Advisory Group** (ISAG), the **RESCEU Ethics Advisory Committee** (EAC) and the **RESCEU Patient Advisory Board** (PAB).

Figure 3. Governance structures in RESCEU.



12. APPENDIX 2: Glossary of Terms

According-To-Protocol (ATP) cohort: This cohort will include all cases enrolled in the study who meet the criteria defined in the protocol for the considered analysis.

Acute respiratory tract infection (ARTI): symptoms of an upper and/or lower respiratory tract infection, such as runny or blocked nose, coughing, fast breathing, chest indrawing, shortness of breath, low oxygen saturation.

Cohort study: A form of epidemiological study where subjects in a study population are classified according to their exposure status/disease and followed over time (prospective/ retrospective) to ascertain the outcome(s).

Epidemiological study: An observational or interventional study without administration of medicinal product(s) as described in a research protocol.

Evaluable: Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the According-To-Protocol (ATP) analysis (see Section 9.3 for details on criteria for evaluability).

Health Burden: Burden of the disease imposed on the study population in terms of incidence of the disease and associated healthcare utilization in any healthcare setting.

Healthcare settings (Healthcare Utilization): Primary, secondary and tertiary care settings such as self-care with over-the-counter [OTC] drugs, general practitioner (GP) visits, emergency room (ER) visits, hospital visits, etc.

Interventional Human Subject Research:
Studies in which participants are administered medical care, medicinal products and/or medical/scientific procedures as described in a research protocol.

Lost-to-Follow-up is defined as no contact by the subject's parent(s)/LAR(s) over the period of 3 planned contacts and/or 2 months and after a final attempt has been made by mail. Once this has been reached, the subject is censored at the time of last contact.

Sponsor: The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.

Prospective study: A study in which the subjects/cases are identified and then followed forward in time in order to address one or more study objectives.

Research protocol: A document that describes the objective(s), design, methodology, statistical considerations, and organization of a study. The protocol usually also gives the background and rationale for the study, but these could be provided in other protocol referenced documents.

Seroprevalence: The total number of cases within the study population at a specific time that test positive for the disease based on blood serum specimens.

Study population: Sample of population of interest.

Sub-cohort: A subgroup of the total cohort of study participants for whom the planned study procedures are different from those planned for the other study participants.

Participant: Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the epidemiological study or a person about whom some medical information has been recorded in a database.

Participant number: A unique number identifying a subject, assigned to each participant consenting to participate in the study.

Surveillance: The ongoing systematic collection, collation, analysis, and interpretation of descriptive epidemiological health data on a specific disease. Surveillance can monitor incidence and/or prevalence, and/or inform about when and where health problems are occurring and who is affected.

13. APPENDIX 3: Clarification of exclusion criteria based on immunosuppression

Exclusion criteria based on immunosuppression related exclusion criteria are as follows:

- Exclusionary immunosuppressive conditions: “Any known or suspected immunosuppressive condition, acquired or congenital, as determined by history and/or physical examination.”
- Exclusionary immunosuppressive medications: “Chronic administration (defined as more than 14 continuous days) of immunosuppressants or other immune-modifying drugs within 6 months prior to study participation. The use of topical, inhaled, and nasal glucocorticoids will be permitted.”

Below is a non-exhaustive list of immunosuppressive conditions and immunosuppressive medications/therapies that are exclusionary according to above two exclusion criteria:

A) Potential subjects with HIV infection, regardless of whether the subject is receiving anti-retroviral treatment.
B) Potential subjects with congenital immunodeficiencies.
C) Potential subjects with active leukemia, lymphoma, or other hematologic malignancy according to following criteria:
    i. Disease known to be present and active (previously treated patients with no evidence of active disease in the previous 6 months are acceptable, provided they meet the requirements for no ongoing cytotoxic drug therapy).
    ii. With or without ongoing therapy.
D) Potential subjects with any prior history of hematopoietic stem cell transplantation.
E) Potential subjects with certain medical conditions (for example, but not limited to, solid tumors/malignancies, or solid organ transplant recipients) requiring any of the following ongoing:
    i. Cytotoxic drug therapy ongoing or within 6 months prior to study participation
    ii. Systemic glucocorticoids in excess of the limits of the protocol (≥10mg of prednisone per day or equivalent for more than 14 continuous days within 6 months prior to study participation)
    iii. Chronic immunosuppressant therapies ongoing or within 1 month prior to study participation to manage solid organ transplants: Calcineurin Inhibitors (e.g. Tacrolimus and Cyclosporine), Antiproliferative agents (e.g. Mycophenolate Mofetil, Mycophenolate Sodium and Azathioprine), mTOR inhibitor (e.g. Sirolimus, Tacrolimus), and/or steroids (e.g. prednisone)
F) Potential subjects with end-stage renal failure or hepatic failure

The following potential subjects should NOT be excluded from participation:

1) Potential subjects with known or suspected "autoimmune diseases" who are untreated or treated with immunomodulatory monoclonal antibodies/biologicals and who have NOT had opportunistic infections.