

101034339 – PROMISE

Preparing for RSV Immunisation and Surveillance in Europe

WP2 – Preparation for future RSV product assessment

D2.3 Report on various effectiveness endpoints for clinical outcomes in RSV studies

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Definitions

- **Participants** of the PROMISE Consortium are referred to herein according to the following codes:
 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.** Terveysten ja hyvinvoinnin laitosp (Finland)
 7. **RIVM.** Rijksinstituut voor Volksgezondheid en Milieu (Netherlands)
 8. **NIVEL.** Stichting Nederlands Instituut voor Onderzoek van de Gezondheidszorg (Netherlands)
 9. **TUCH.** Varsinais-Suomen sairaanhoitopiirin 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
ARI	acute respiratory infection
CHF	congestive heart failure
COPD	chronic obstructive pulmonary disease
ECDC	European Centre for Disease Prevention and Control
GAM	General Assembly Meeting
ICD-10	International Classification of Diseases, 10 th revision
ICPC2	International Classification of Primary Care, 2 nd edition
ICU	intensive care unit
ILI	influenza-like illness
LRTI	lower respiratory tract infection
NITAG	National Immunization Technical Advisory Group
OTC	over-the-counter
RSV	respiratory syncytial virus
SARI	severe acute respiratory infection
SpO₂	oxygen saturation
WHO	World Health Organization

Abstract

Using similar endpoints in clinical RSV studies (both clinical trials and observational studies) is crucial for the comparability of the efficacy or effectiveness of different products. Furthermore, the use of standardized endpoints helps determine the comparative cost-effectiveness of interventions in the society.

We have reviewed endpoints used in previous clinical studies in the field of RSV and influenza and the strengths and limitations of each endpoint. This document is intended as a starting point for discussions between public health and private stakeholders and will feed into later PROMISE outputs, including study protocols.

Future work (backed by a full systematic review of endpoints used in literature and stakeholder consultation) could classify endpoints further e.g., based on specificity and clinical relevance as well as pragmatism and cost-efficiency of studying them.

1. Introduction

In evaluating various products for prevention or treatment of RSV, it is crucial to choose the most appropriate clinical outcomes. Establishing common endpoints is needed for the comparability of the efficacy or effectiveness of different products with the same indication, and it also helps national and regional decision-makers in determining the cost-effectiveness of various interventions.

Clinical studies of RSV products can be performed in multiple settings and using different study designs. Also, the intended use of the study data might drive the selection of the endpoints. For example, a regulatory agency considering the authorization of a product can have partially different data needs than a public health body considering the adoption of a product in a national immunization program. Because the products aimed against RSV are relatively new, it is also useful to look at the endpoints used in studies of more established products against other respiratory viruses, notably against influenza viruses.

Endpoints can be categorized along several axes. There are endpoints with and without laboratory confirmation of RSV, in outpatient and inpatient settings, in cases of varying severity, across several categories of age, comorbidity, and pregnancy, and in observational studies or randomized trials looking at different types of products. On top of these individual health outcomes, there are even more general outcomes such as over-the-counter medication sales and school absenteeism which may be of interest to national and regional decision-makers.

2. Methods

This deliverable includes a list of efficacy and effectiveness endpoints that have been used in previous RSV product studies. Because influenza is currently the viral respiratory infection with the most products available for its prevention and treatment, we have also reviewed endpoints used (or hypothesized) in influenza product studies. The list was initially collated by THL and TUCH as a non-systematic literature review, and it was elaborated on at a specific workshop that was held during the third PROMISE General Assembly Meeting (GAM) in Brussels on 7 September 2022.

Endpoints have been described with both experimental trials and observational studies in mind. The list aims to cover endpoints that are relevant to studies of vaccines, monoclonal antibodies, and antivirals.

Discussions at the GAM workshop emphasized the different needs of various stakeholders regarding the endpoints. For the purposes of this deliverable, we present the general strengths and limitations of each endpoint but refrain from any preferential recommendations. Also, the study designs used to capture product efficacy/effectiveness (such as test-negative design, cohort, and screening method studies) come with their own strengths, weaknesses, and capacity to address bias. These methodological questions are outside the scope of this document.

We have intentionally included a wide variety of endpoints including ones less relevant for direct measurement of product efficacy/effectiveness, recognizing that not all of them will be relevant to all audiences. Any given study should specify its endpoints and case definitions in a robust way.

3. Results

3.1. Summary table

	Infants and children	Adults (including pregnant women and older adults)
Clinical symptom with laboratory-confirmed RSV	<ul style="list-style-type: none"> • Any RSV infection • Lower respiratory tract infection (LRTI) • Medically significant LRTI • LRTI with severe hypoxemia • Mortality due to RSV • Otitis media • Long-term sequelae of RSV infection (e.g., asthma) 	<ul style="list-style-type: none"> • Any RSV infection • Lower respiratory tract infection (LRTI) • Medically significant LRTI • LRTI with severe hypoxemia • Mortality due to RSV • Exacerbation of chronic pulmonary condition • Cardiovascular events • Long-term sequelae of RSV infection (e.g., frailty)
Healthcare contact with laboratory-confirmed RSV	<ul style="list-style-type: none"> • Outpatient visits • Hospitalization • Admission to ICU • Length of stay in hospital or ICU • Any medically attended RSV infection • Antibiotic treatment 	<ul style="list-style-type: none"> • Outpatient visits • Hospitalization • Admission to ICU • Length of stay in hospital or ICU • Any medically attended RSV infection • Antibiotic treatment
Patient-reported outcome with laboratory-confirmed RSV	<ul style="list-style-type: none"> • Parental work absenteeism 	<ul style="list-style-type: none"> • Work absenteeism
Miscellaneous (no laboratory confirmation of RSV)	<ul style="list-style-type: none"> • Outpatient visits for ARI • Hospitalization for SARI or all-cause LRTI • All-cause LRTI • OTC medication sales • Social media and search engine trends • Virus shedding in wastewater 	<ul style="list-style-type: none"> • Outpatient visits for ARI • Hospitalization for SARI or all-cause LRTI • All-cause LRTI • OTC medication sales • Social media and search engine trends • Virus shedding in wastewater

3.2. Endpoints

3.2.1. Outpatient visits (laboratory-confirmed RSV)

Background

- Laboratory-confirmed viral infection in outpatient settings has been used as an endpoint in vaccine efficacy/effectiveness studies (e.g., influenza)

Strengths

- RSV-specific outcome
- Cost-efficient to study (especially using register-based and screening methods)
- The test-negative design has the added benefit of controlling, by study design alone, for certain types of bias, particularly bias from health service seeking (Sullivan et al. 2016)
- Can also catch frequent complications of RSV (e.g., acute otitis media, sinusitis) that are usually treated only in the outpatient setting (Thomas et al. 2021)
- For register-based studies, data availability for the entire population 1) minimizes selection and recall bias, 2) allows outcome evaluation over a long time period, 3) increases statistical power, 4) ensures representativeness of the target population in a real-world setup, 5) permits undertaking stratified analysis among a sub-population of concern such as individuals with low socioeconomic status (Thygesen et al. 2014)

Limitations

- Currently, little RSV testing is being performed in most outpatient settings. In many countries, this will be limited to surveillance sites, in which case the sample size may be too limited for product efficacy/effectiveness estimation
- A common definition of an outpatient visit is needed as there is some ambiguity e.g., regarding whether hospital emergency room visits should be included (emergency room visits could be considered a separate endpoint)
- No standard definition for time since laboratory-confirmed RSV infection

3.2.2. Hospitalization with RSV-associated LRTI

Background

- Frequently used in RSV studies (e.g., Griffin et al. 2020, Madhi et al. 2020)
- Usually requires virologic confirmation of RSV plus hospitalization with symptoms of lower respiratory tract infection
- Clinical RSV testing may have increased during the COVID-19 pandemic in some areas (although it is not yet known if this is a lasting trend)

Strengths

- RSV-specific outcome
- Hospitalization is a clinically important outcome implying increased severity of infection
- Relevant for all age groups
- Hospitalization cost is often a key driver of the cost-effectiveness of an intervention

Limitations

- Includes also patients hospitalized with non-severe RSV (e.g., for social reasons or the presence of underlying medical conditions placing the patient at potential risk of increased severity or complications)
- The threshold for hospitalization may vary between different areas/countries
- Attaining a sufficient sample size relies on the amount of clinical testing
- In non-register-based studies, access to health care and health-seeking behavior could present a limitation

3.2.3. Medically significant RSV LRTI

Background

- Frequently used in RSV studies for children (e.g., Madhi et al. 2020)
- Usually requires evidence of lower respiratory tract involvement (e.g., rhonchi, rales, wheeze), increased respiratory rate, hypoxemia ($O_2 < 95\%$ or $< 92\%$ at high altitude), and clinical signs of severe respiratory disease (e.g., apnea, retractions, dehydration due to respiratory distress)
- Medically significant does not necessarily imply hospitalization, so cannot be used as a proxy for hospitalization

Strengths

- RSV-specific, clinically important outcome
- Includes the majority of patients (especially children) hospitalized with RSV infection
- Largely independent from socioeconomic settings

Limitations

- “Medically significant” has not been clearly defined
- Oxygen saturation may change and fluctuate rapidly during the course of illness, so the measurement is dependent on the timing of the procedure
- Generally used O_2 limits for hypoxemia (e.g., $< 95\%$ or 92%) are arbitrary and may not indicate true clinically meaningful thresholds
- The choice of cut-off points (e.g., for SpO_2) can impact the results significantly: for meaningful comparisons everyone should use the exact same criteria
- SpO_2 is not always available in retrospective studies
- Generally used adjustment for altitude ($<$ or > 1800 m) is also arbitrary

3.2.4. RSV-associated LRTI with severe hypoxemia

Background

- Has been used in RSV studies but usually as a secondary outcome (Madhi et al. 2020)
- Many patients with severe hypoxemia (often defined as $O_2 < 92\%$ or $< 87\%$ at high altitude) may be treated in the intensive care unit (ICU)

Strengths

- RSV-specific outcome

- Includes patients with the most severe clinical presentations that would especially need to be prevented or treated effectively

Limitations

- Represents a minority of hospitalized patients, so requires relatively large sample sizes to demonstrate efficacy/effectiveness
- Difficult to operationalize because of rapid fluctuation of saturation in patients
- Generally used O₂ limits for severe hypoxemia (<92% or <87% at high altitude) are arbitrary
- Generally used adjustment for altitude (< or >1800 m) is also arbitrary
- In some settings with limited healthcare resources, patients with severe hypoxemia may not have access to an ICU

3.2.5. Admission to ICU for RSV-associated LRTI

Background

- Included as an outcome especially in studies among infants and children

Strengths

- RSV-specific outcome
- Includes the most severe manifestations of RSV
- Treatment in the ICU is generally the most expensive part of hospitalization

Limitations

- Some patients may enter the ICU for other reasons than severe clinical manifestations of RSV (e.g., lack of regular hospital beds during an epidemic, need for follow-up due to underlying medical condition, etc.)
- Represents a minority of hospitalized patients, so requires relatively large sample sizes to demonstrate efficacy/effectiveness
- Criteria of ICU admission vary between areas and countries
- Being relatively rare, ICU episodes represent only a fraction of all societal costs of RSV and thus are less relevant for cost-effectiveness assessment

3.2.6. Length of stay at hospital (or ICU) for RSV-associated illness

Background

- Often used as an outcome in treatment trials (e.g., with antivirals)

Strengths

- Length of stay has a direct impact on hospitalization costs and furthermore on the cost-effectiveness of an intervention
- Measured as a continuous variable, the power to demonstrate differences between groups is higher than for dichotomic outcomes (yes/no)
- Useful outcome especially for RSV antiviral trials in which patients have been already hospitalized

Limitations

- Does not automatically indicate the true need for hospitalization because many other factors affect the actual time of discharge
- Stratification by comorbidities is necessary
- Duration of hospitalization may vary substantially between different areas/countries because of tradition or other reasons
- Indirect costs such as absenteeism, daily living expenses, decreased productivity, and time needed to resume work activities are not often measured

3.2.7. Mortality due to RSV

Background

- Mortality is a frequently used outcome in infectious diseases and medicine in general
- Can be ascertained from death certificates or health registers (e.g., all-cause deaths during a follow-up time period since positive RSV test)
- The length of follow-up must be harmonized in the case definition

Strengths

- Death is usually the worst possible outcome that would need to be prevented
- Can be relatively easily confirmed in most areas/countries

Limitations

- RSV-related deaths are very rare among children, especially in high-income countries
- Death after the diagnosis of RSV may not necessarily prove that RSV was the cause of death
- In adults, the downstream complications of RSV, such as exacerbation of chronic obstructive pulmonary disease (COPD) or congestive heart failure (CHF), rather than RSV itself, can be more likely to be included as cause of death
- Measuring death events requires a large sample size to draw firm conclusions
- No standard definition for time since laboratory-confirmed RSV infection

3.2.8. Any medically attended RSV infection

Background

- In some countries or regions, register data on positive RSV tests may be available but without indication of why and where the test was taken

Strengths

- Cost-efficient study design if data is readily available

Limitations

- Dependence on availability and completeness of registers, risk of bias (see also: Outpatient visits)
- Resulting overall vaccine efficacy/effectiveness is less specific
- Some countries do not track tests taken but just positive tests, which does not allow for adjustments for number of tests performed, which varies across the year and from year to year.

- In many settings, very few tests are performed among adults

3.2.9. Antibiotic treatment post confirmed RSV

Background

- Patients with RSV may be prescribed antibiotics, either unnecessarily or because of actual confirmed or suspected secondary bacterial infection

Strengths

- Enriches the understanding of RSV burden and product efficacy/effectiveness
- Whether the antibiotic treatment is correctly indicated or not, prevention of RSV-associated antibiotic prescribing is desirable as it either means reducing secondary infections or overprescribing

Limitations

- Data availability
- Highly impacted by local practices on antibiotic use
- Patient adherence to antibiotic treatment guidelines in case of non-hospitalized patients might introduce a bias

3.2.10. Otitis media

Background

- Middle ear infections are common following RSV infection (Heikkinen et al. 1999, Thomas et al. 2021)

Strengths

- Enriches the understanding of RSV burden and product efficacy/effectiveness
- Prevention of otitis media is desirable as it may reduce disease burden, parental work absenteeism, antibiotic prescribing, and costs of treatment

Limitations

- Data availability

3.2.11. Long-term sequelae of RSV infection

Background

- An association has been observed between early life RSV infection and subsequent recurrent wheeze or asthma (Pérez-Yarza et al. 2007, Shi et. al 2020); these are mostly diagnosed and treated in the outpatient setting
- It is conceivable that sequelae may also be found in the adult population (such as increased frailty after RSV infection) (Branche et al. 2022a)
- Adults are at increased risk for readmission during the months following RSV hospitalization (e.g., Falsey et al. 2021)

Strengths

- Any observed decrease in long-term pulmonary effects or frailty would be of public health importance and also relevant to cost-effectiveness calculations

Limitations

- A follow-up time up to several years may be required
- Establishing a connection with laboratory-confirmed RSV may be difficult

3.2.12. Exacerbation of chronic pulmonary condition

Background

- RSV may cause more severe illness in patients with chronic pulmonary conditions

Strengths

- Public health significance

Limitations

- Limited added value compared to product efficacy/effectiveness against hospitalization
- No clear case definition to distinguish RSV from other causes of hospitalization
- No standard definition for time since laboratory-confirmed RSV infection

3.2.13. Cardiovascular events

Background

- Myocardial infarction has been associated with influenza and, at least to some degree, RSV infection (Kwong et al. 2018) and COVID-19 (Katsoularis et al. 2021). Influenza vaccination has been linked to reduced cardiovascular risk (Behrouzi et al. 2022).
- Nearly all RSV hospitalization incidence studies (e.g., Falsey et al. 2005, Branche et al. 2022b) include CHF exacerbations as a clinical syndrome to prompt RSV testing

Strengths

- Public health significance

Limitations

- Represents a narrow subcategory of RSV disease burden that is largely captured in RSV-related hospitalizations
- No standard definition for time since laboratory-confirmed RSV infection

3.2.14. Outpatient visits for ARI

Background

- Acute respiratory infection is a symptomatic definition that can be used for surveillance purposes. Influenza-related work has used influenza-like illness (ILI); prominent case definitions include those by the WHO and ECDC (WHO 2014, ECDC 2018). However, ILI case definitions commonly include fever, whereas, in a WHO surveillance pilot, a case definition without fever substantially increased the number of RSV infections detected (WHO b).

- Data on cases and their vaccination status can be captured e.g., in a family doctor network using agreed case definitions or in a register-based manner, looking at healthcare visits with certain ICD-10 or ICPC2 codes and linkage with vaccination registers
- RSV is a frequent cause of ARI, although its relative role among various viruses in different populations has not been completely characterized

Strengths

- Syndromic surveillance is already established in many countries and regions, and existing systems could be harnessed for vaccine effectiveness studies with little extra effort
- Burden of disease from ARI is considerable. Even modest demonstrable effectiveness against ARI could have major public health implications.
- Unlike hospital settings where RSV burden is most pronounced in infants and the elderly, outpatient settings can capture clinical illness across all ages and population groups.

Limitations

- Nonspecific. As many pathogens can cause ARI, vaccine effectiveness against ARI is bound to underestimate the effectiveness against RSV specifically (though this could be alleviated by restricting analysis to the RSV season when more cases are expected to be due to RSV)
- Current surveillance schemes have been developed with influenza in mind and commonly use ILI. While the symptoms overlap with RSV, ILI is not suitable for RSV surveillance as many infections do not present with the required symptoms for the ILI case definition (e.g., fever) (Korsten et al. 2022).
- In countries near the equator, there may be challenges and methodological limitations with less clear-cut RSV seasonality

3.2.15. Hospitalization with SARI or all-cause LRTI

Background

- Common non-specific clinical outcomes in influenza vaccine effectiveness studies (e.g., Valenciano et al. 2008)
- Data collection from hospital discharge registers, medical records
- Similar non-specific outcomes (e.g., all-cause community-acquired pneumonia hospitalizations) have been used for pneumococcal vaccines

Strengths

- Data availability, may be collected from electronic registries
- Does not depend on standard-of-care RSV testing which among adults may be infrequent and miss infections even among those tested

Limitations

- Non-specific; without confirmation of pathogen, likely to underestimate vaccine effectiveness (but if able to document significant reductions, public health impact would be large)
- In countries near the equator, there may be challenges and methodological limitations with less clear-cut RSV seasonality

3.2.16. All-cause LRTI

Background

- Please see *Hospitalization with SARI or all-cause LRTI (3.2.15)*
- Sometimes the diagnosis of pneumonia or other lower respiratory infection is available from health registers without knowledge of the setting it was treated in

Strengths

- As with all-cause LRTI (3.2.15)

Limitations

- As with all-cause LRTI (3.2.15) but with lack of specificity further emphasized
- In countries near the equator, there may be challenges and methodological limitations with less clear-cut RSV seasonality

3.2.17. Work / school absenteeism

Background

- Although outpatient RSV infections are generally mild, they are frequently associated with parental work absenteeism or work absenteeism that may have substantial impacts on the cost-effectiveness of an intervention from the societal perspective (Heikkinen et al. 2017)
- School absence data has been proposed as an outcome in estimating influenza vaccine effectiveness (Stuurman et al. 2018)

Strengths

- Potential to detect underreported burden of symptomatic RSV

Limitations

- Highly unspecific
- Working-age adults and school-aged children are not primary target groups for current RSV products
- Not all countries or regions have a reliable tracking system

3.2.18. Over-the-counter medication sales

Background

- Data on OTC medication sales (such as cough and cold medicines) or antibiotics may be indicative of the general burden of infections (Liu et al. 2013)

Strengths

- Potential to detect underreported burden of symptomatic RSV

Limitations

- Highly unspecific
- Data availability and comprehensiveness likely to vary
- Unprescribed antibiotics can be obtained without prescription in some countries

- Acquiring unprescribed drugs from the pharmacy might bias the RSV burden, as symptoms might be due to other infections
- Some drugs can be obtained from one's social environment (friends, family) and might not be reflected in medication sales, causing an underestimation of the burden of infections
- In individuals with limited economic resources and in countries where medications are not reimbursed, medications are not always accessible to patients

3.2.19. Social media and search engine trends

Background

- There have been attempts to use search engine queries, Twitter, and other social media platforms to track ILI (Stuurman et al. 2018).

Strengths

- Timely and low-cost study method
- Potential to detect underreported burden of symptomatic RSV

Limitations

- Highly unspecific. For example, a search may not reflect an actual RSV episode but just general or media interest in the illness and/or products against it (although there is some chance advanced computational methods such as machine learning could alleviate this)
- Difficulty linking with vaccination data
- Data are limited to individuals with access to the internet and electronic facilities (mobile, computer)
- Inability to adjust for sociodemographic and socioeconomic factors

3.2.20. Virus shedding in wastewater

Background

- Viruses can be detected in wastewater samples. This has been used in surveillance of polio (WHO 2003) as well as during the COVID-19 pandemic (Shah et.al. 2022)
- Detection of RSV in wastewater has been demonstrated (Hughes et al. 2022)

Strengths

- Timely and low-cost study method
- Potential to detect underreported burden of RSV
- Data not reliant on testing activity

Limitations

- Widespread RSV wastewater testing has not been established
- Robust demonstration of causality with product use is likely impossible
- Would require sampling to begin prior to vaccine introduction

4. Discussion

In this report, we have critically reviewed the endpoints that have been frequently used in clinical studies in the field of RSV and influenza, together with the strengths and limitations of each endpoint. Besides RSV-specific endpoints, we have also considered some other endpoints that might have great public health importance.

The initial list of endpoints was discussed at a specific workshop organized during the PROMISE GAM in Brussels in September 2022. Following the meeting, a modified document was circulated among the attendees of the workshop to invite further comments and suggestions regarding the endpoints, their strengths, and limitations. Based on the discussions, it has become clear that the endpoints for clinical studies of various future products need to be tailored according to multiple factors, such as age, comorbidity, setting, and the type of product being investigated. Furthermore, to be really useful for the future assessment of various products, there is a strong need to also acquire the opinions of regulatory agencies and national immunization technical advisory groups (NITAGs) on what they consider as most important in their own evaluations and decision-making. In addition to determining the most useful endpoints, there is also a need to harmonize various case definitions.

In light of the above, the current document should be regarded as an interim report that serves as a basis for further discussions and consultations among the various stakeholders in the field. Considering the great importance of selecting the most useful endpoints for the future, this work will be also supported by a full systematic literature review of endpoints used in studies.

5. Conclusion and next steps

This interim report serves as the basis for further discussions and consultations between different stakeholders in the RSV field. To support those discussions, a full systematic literature review of endpoints used in studies will be performed. A final report of the most useful endpoints for various types of studies and products will be provided following further consultations among all stakeholders.

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