



101034339 – PROMISE

Preparing for RSV Immunisation and Surveillance in Europe

WP2 – Preparation for future RSV product assessment

## D2.5 Report on consultations with Health Authorities on data elements needed for Phase IV studies

<b>Lead contributor</b>	Topi Turunen (6 – THL) topi.turunen@thl.fi
<b>Other contributors</b>	Hanna Nohynek (6 – THL) Francesca Rocchi (14 – PENTA)
<b>Reviewers</b>	Public - Javier Díez-Domingo (15 – FISABIO), Private - Tin Tin Htar (21 – Pfizer) Advisor/Public - Anne Teirlinck (7 – RIVM)

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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.** 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 sairaanhoitopiirin kuntayhtymä (Finland)
  10. **TEAMIT.** TEAM IT Research, S.L. (Spain)
  11. **ReSViNET.** Stichting Resvinet (Netherlands)
  12. **SSI.** Statens Serum Institut (Denmark)
  13. **SERGAS.** Servicio 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
<b>ECDC</b>	European Centre for Disease Prevention and Control
<b>EFPIA</b>	European Federation of Pharmaceutical Industries and Associations
<b>ETF</b>	Emergency Task Force
<b>EU</b>	European Union
<b>GAM</b>	General Assembly Meeting
<b>mAb</b>	Monoclonal antibodies
<b>NITAG</b>	National Immunization Technical Advisory Group
<b>RSV</b>	Respiratory syncytial virus
<b>WHO</b>	World Health Organization
<b>WP</b>	Work Package

## Abstract

Understanding the efficacy, effectiveness, and safety of RSV preventive products (i.e., monoclonal antibodies and vaccines) is relevant to a wide variety of health authorities, from regulators to public health institutes and international health agencies. The PROMISE Consortium has undertaken consultations with public health stakeholders about their data needs when getting ready to make decisions on the introduction of new RSV preventive products. The Consortium's outputs that in particular have been subjected to external review are the evaluation of clinical endpoints in RSV studies and the generic product effectiveness study protocols.

In conclusion, consultations with health authorities have resulted in important feedback. Given that many member states have not yet decided how RSV products will be assessed and that it will take time before PROMISE's generic research protocols can be applied in practice, further consultations may be necessary in the future, possibly even during the remaining contract period of the PROMISE Consortium.

## Introduction

The efficacy, effectiveness, cost-effectiveness, and safety of preventive products against RSV, i.e., vaccines and monoclonal antibodies (mAbs), is of interest to many public health stakeholders. However, the data needs of the different health authorities can differ. For example, a regulatory agency considering the authorization of a product can have partially different data needs (pre- and post-licensure efficacy and safety) than a public health body considering the adoption of a product in a national immunization program (efficacy, effectiveness, safety, indirect population level impact, cost-effectiveness).

As with vaccines and other preventive products in general, providing appropriate efficacy and effectiveness data is further complicated by the fact that RSV preventive product studies can be performed in multiple settings, using different study designs, looking at various endpoints and incorporating different covariates, and that different data may be available in various countries depending on local research networks, surveillance systems or electronic databases. An optimal research strategy thus requires thorough understanding of available data and stakeholder needs.

To ensure that PROMISE's outputs will be relevant to as many health authorities as possible, PROMISE's Work Package (WP) 2 has undertaken consultations with public health stakeholders, a summary of which is presented in this document.

## Methods

Consultations with health authorities have mainly concerned three project outputs:

1. Report on various effectiveness endpoints for clinical outcomes in RSV studies (D2.3)
2. Generic protocol for effectiveness of vaccines and monoclonal antibodies against medically attended respiratory syncytial virus infection: Test negative case control study (part of D2.6)
3. Effectiveness of vaccines and monoclonal antibodies against respiratory syncytial virus: Generic protocol for register-based cohort study (part of D2.6)

The consultation process aimed to address all currently envisioned approaches and target groups for RSV prevention (mAbs and vaccines; children, older adults and maternal immunization).

The consultatory work commenced with an internal workshop about clinical endpoints at the PROMISE General Assembly Meeting in Brussels in September 2022. The listing and evaluation of endpoints were based on expert opinion and non-systematic literature review. Following the meeting, a draft of the endpoints document was circulated among the attendees to invite further comments and suggestions regarding the endpoints, their strengths, and limitations.

The endpoints document was completed in November 2022 and was submitted for review and comments to the European Medicines Agency's Emergency Task Force (EMA ETF) after WP2 held a consultatory meeting with the EMA ETF on 31 January 2023. Written feedback was requested from the EMA ETF.

Work on PROMISE's effectiveness study protocols began with a review of existing protocols in November 2022. These included test-negative design (TND) and cohort study protocols for influenza, rotavirus and COVID-19 vaccine effectiveness (COVIDRIVE, 2022) (THL, 2021) (DRIVE, 2021) (I-MOVE+, 2015) (I-MOVE+, 2015) (I-MOVE+, 2015) (Hollingsworth R et al., 2021) (Domingo-Diez J et al., 2020) (Layton B et al., 2020) (I-MOVE, 2019) (ECDC, 2013), (ECDC, 2013) (ECDC, 2013). Project partners RIVM and THL then went on to develop the TND and register-based cohort study protocols, respectively.

A draft version of the generic product effectiveness study protocols was the subject of another remote consultation meeting that was held with national public health institutes and National Immunization Technical Advisory Groups (NITAGs) on 30 March 2023. Representatives were also invited from the European Centre for Disease Prevention and Control (ECDC), World Health Organization (WHO), WHO-European region, WHO Headquarters as well as EMA. A pre-meeting survey (Annex 1) was sent out to capture information on current and planned assessment of RSV vaccines and mAbs in European Union (EU) member states.

## Results

### European public health institutes

A teleconference on research needs related to RSV was held on 30 March 2023. A total of 81 professionals from across Europe participated out of 173 invited, representing a variety of national and international public health institutes, NITAGs and laboratory and surveillance professionals.

The agenda (Annex 2) consisted of an introduction of PROMISE and its RSV surveillance network, presentations on the two product effectiveness study protocols followed by a discussion on research priorities in product effectiveness studies. Among the topics discussed were the pros and cons of the test-negative design (TND) and cohort studies when studying product effectiveness against RSV, potential interaction with product effectiveness against influenza and COVID-19, and the importance of using control outcomes.

A pre-meeting survey (Annex 1) to which 10 out of 27 member states had replied also collected information about how RSV vaccines and mAbs were being assessed in European Union (EU) member states and what future effectiveness or safety studies were planned. The results indicated that as of March 2023, many member states do not yet have concrete plans for evaluation of RSV products.

The generic study protocols had been circulated to the participants beforehand and they had until 11 April 2023 to give feedback. Other meeting materials included the clinical endpoints document (D2.3) and the Rules of Collaboration of PROMISE, thought to be informative to the public health institutes and allowing them to better understand the firewalling processes of the PROMISE materials and the contributions of the European Federation of Pharmaceutical Industries and Associations (EFPIA) partners.

### EMA

An introductory meeting was held between PROMISE and the EMA ETF on 31 January 2023 which focused on a presentation of the Consortium and its WP2. During the meeting, it was clarified that PROMISE would not actually perform post-licensure studies but would provide generic protocols to be tailored to stakeholder needs. There was mutual understanding on the need of clearly defined endpoints and case definitions. Possible collaboration with EMA-ECDC Vaccine Monitoring Platform was discussed as well as some other topics not solely limited to preventive product efficacy and effectiveness; these included genomic surveillance, biomarkers and concerns on immune escape.

After the meeting, the EMA ETF proceeded to provide brief comments on PROMISE's endpoints document (Annex 3). These highlighted that endpoints need to be tailored to the intended use and that a comprehensive description of the reasons for choosing or not choosing the endpoints in specific context needs to be provided, as well as the importance of case definitions. The EMA ETF also remarked that time-to-clinical recovery or symptoms resolution and endpoints that include parents'/caregivers' contribution in the outpatient setting (e.g., ReSViNET scale for parents) seemed to be missing from the list.

The EMA ETF also reminded that guidelines for reference in the EU exists (EMA, 2017). The EMA was invited to the aforementioned meeting of the public health institutes and NITAGs and asked for feedback on PROMISE's generic effectiveness study protocols. As of 26 April 2023, no feedback on

the protocols has been received.

## **ECDC**

PROMISE asked for ECDC's cooperation on organising the public health institutes' and NITAGs consultation meeting. However, the ECDC has decided to limit their cooperation with PROMISE to Tasks 2.1 and 2.2 and not Task 2.3 concerned in this deliverable. ECDC did not participate in the 30 March 2023 consultation meeting.

The same project outputs and invitations to the public health institutes' teleconference have been shared with ECDC representatives but as of 26 April 2023, no feedback has been received.

## **WHO**

A subject matter expert from the WHO provided some feedback early in the study protocols' planning phase. This included advice on clinical outcomes and what existing protocols to look into when commencing the writing process. They also participated in the 30 March 2023 teleconference.

Experts from the WHO-European region have been provided with the same project outputs but as of 26 April 2023, no feedback has been received.

## Discussion

Receiving and implementing external feedback is crucial to ensure the usability and acceptability of the outputs of the PROMISE Consortium. A multipronged approach with many different health authorities has resulted in important feedback to PROMISE's generic research protocols.

The process of consulting member states and EU institutions was somewhat slower than expected. This was partially due to the initial ambivalence over ECDC's role in the process. After the ECDC made clear they would not extend their involvement to study protocol consultancy, PROMISE was able to approach member states more directly through an independently organized webinar.

Several aspects suggest that further consultations and revisions of PROMISE outputs may be necessary in the future, possibly even during the contractual period of the Consortium. For now, no input has been received from the ECDC and WHO-European region, and EMA's input (Annex 3) has been relatively high-level. Consultations with member states have shown that many countries have not yet completely aligned on how RSV products will be assessed. A comprehensive picture of RSV-specific disease surveillance is only forming in the EU. Furthermore, it will still take some more time before RSV preventive products will become widely available, and some development needs of the generic research protocols may only become apparent when they can first be applied in practice.

PROMISE will continue to interface with important health authorities in the EU over the remaining project period to help make its outputs as relevant as possible for the European public health community.

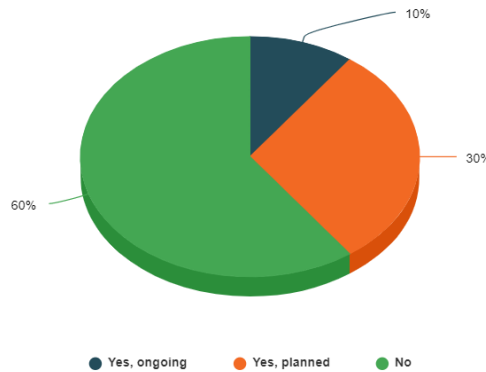
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- DRIVE. 2021.** *D7.1.3 Core protocol for type/brandspecific influenza vaccine.* 2021.
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- I-MOVE+. 2015.** *Generic Protocol for measuring the impact of influenza vaccination programmes among the elderly population in the European Union and European Economic Area Member States.* 2015.
- . **2015.** *Generic Protocol for measuring the impact of influenza vaccination programmes among the elderly population in the European Union and European Economic Area Member States.* 2015.
- . *Generic Protocol for the Test Negative Design case control studies to measure pandemic and seasonal influenza vaccine effectiveness in the European Union and European Economic Area Member States.*
- . **2015.** *Generic Protocol for the Test Negative Design case control studies to measure pandemic and seasonal influenza vaccine effectiveness in the European Union and European Economic Area Member States.* 2015.
- Layton B et al. 2020.** *Real-world effectiveness of <<COVID 19 vaccine product>> in Europe: a protocol template for a cohort study based in existing health care data sources from the ACCESS project.* 2020.
- THL. 2021.** *DRIVE protocol, season 2021/22.* 2021.

**Annex 1. Survey results from 10 EU member states prior to the NITAG consultative meeting on 30 March 2023.**

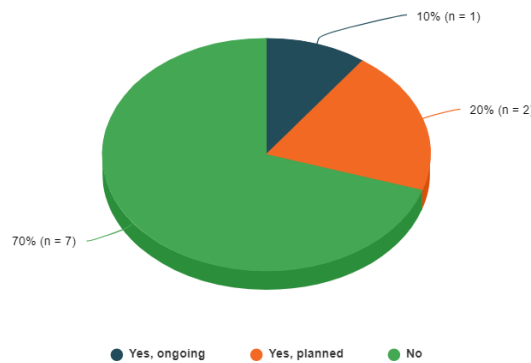
**Is your country conducting or planning cost-effectiveness evaluation or similar on **vaccines** against RSV?**

- *RSV transmission model & cost-effectiveness evaluation with results by summer 2023*
- *Cost-effectiveness evaluation will be done when the vaccine is available, but there are no concrete plans at the moment*



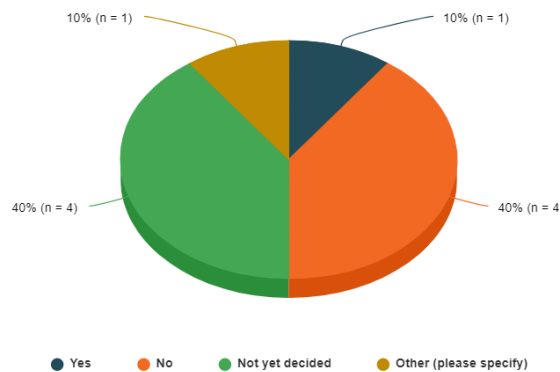
**Is your country conducting or planning cost-effectiveness evaluation or similar on **mAbs** against RSV?**

- *under discussion*
- *results expected this summer*
- *in the process of planning*



**Are you aware of vaccine/mAb effectiveness or safety studies that are planned in your country once RSV vaccines and/or mAbs are available?**

- *consulting other institutions*



## **Annex 2. Agenda of the public health institutes' meeting (30 March 2023)**

*March 30 Consultation on research needs on RSV, Agenda (times CET):*

12:00 Introduction to the PROMISE project (Harish Nair, University of Edinburgh)

12:15 RSV surveillance network (Lance Presser & Adam Meijer, RIVM)

12:35 Ongoing & future RSV product evaluation: survey results (Topi Turunen, THL)

12:45 Protocol for test-negative design studies of RSV products (Caren van Roekel, RIVM)

13:00 Protocol for cohort studies using electronic databases (Eero Poukka, THL)

13:15 Discussion: Research priorities in product effectiveness studies

14:00 Meeting ends

### **Annex 3. Comments from EMA ETF to Effectiveness endpoints document**

16 March 2023

*ETF briefing note on D2.3 Report on various effectiveness endpoints for clinical outcomes in RSV studies provided by the PROMISE consortium*

#### *Summary of topic content*

*On January 31, 2023, a preliminary meeting between ETF members and PROMISE (Preparing for RSV Immunisation and Surveillance in Europe) consortium was held. PROMISE mission is to continue advancing scientific knowledge on Respiratory Syncytial Virus (RSV) to better inform public health strategies and to support the development and monitoring of novel immunisation and therapeutics against this potentially deadly virus in the paediatric and elderly populations. The consortium requested this meeting with EMA/ETF to discuss various issues, including whether the studies resulting in this consortium could be considered under the remit of the Vaccine Monitoring Platform (VMP).*

*The consortium shared a report on various effectiveness endpoints for clinical outcomes in RSV studies, for further feedback from the ETF. For this document, endpoints used in previous clinical studies in the field of RSV and influenza and the strengths and limitations of each endpoint were reviewed.*

#### *ETF recommendations*

*It is acknowledged that the document represents a preliminary work and will be followed by a full systematic literature review of the endpoints used in RSV clinical studies. However, there are some issues that can already be raised that may contribute to the continuation of this exercise. The authors rightly state in the conclusion that each endpoint must be tailored to a number of factors, and, in this regard, it is highly relevant that endpoints are tailored to the intended use and that a comprehensive description of the reasons for choosing or not the endpoints in specific contexts is provided. It would also be relevant to obtain information with respect to different populations and characteristics such as age, disease severity and comorbidities and to describe the endpoints according to study design or the scope of the study as strengths and limitations may apply differently.*

*The definitions used for low respiratory tract infection (LRTI) and disease severity vary, so it would be useful to assess how these different definitions perform and whether there would be options for agreeing on specific case definitions. With respect to the endpoints that include LRTI and disease severity, the assessment of hypoxemia is mentioned as a limitation since its value is dependent on the timing of the procedure and the view that the used limits of oxygen saturation which define hypoxemia are arbitrary. However, this is a sign that can be assessed objectively and could instead be considered a strength provided that (e.g.) its measure is performed under standardised conditions which need to be pre-specified in the study protocol. For pivotal trials, due to the variability in healthcare systems and admission thresholds, it is not advisable to base a judgement of disease severity on the perceived need for hospitalization; however, the number of hospitalizations could be assessed to establish the effectiveness of vaccines in preventing severe disease. Other endpoints such as all-cause mortality, time-to-clinical recovery or symptoms resolution, and endpoints that include parents/caregivers contribution in the outpatient setting (e.g. ReSVinet scale for parents) are missing.*

*From the regulatory point of view in the European Union, the guideline of reference for the topic under discussion is the following: Guideline on the clinical evaluation of medicinal products indicated for the prophylaxis or treatment of respiratory syncytial virus (RSV) disease (EMA/CHMP/257022/2017) Guideline on respiratory syncytial virus (RSV) (europa.eu)*