POSITION PAPER

# Recommendations for assessing Patient-Reported Outcomes and Health-Related quality of life in clinical trials on allergy: a GA$^2$LEN taskforce position paper

I. Baiardini[1], P. J. Bousquet[2], Z. Brzoza[3], G. W. Canonica[1], E. Compalati[1], A. Fiocchi[4], W. Fokkens[5], R. G. van Wijk[6], S. La Grutta[7], C. Lombardi[8], M. Maurer[9], A. M. Pinto[10], E. Ridolo[11], G. E. Senna[12], I. Terreehorst[5], A. Todo Bom[13], J. Bousquet[14], T. Zuberbier[9] & F. Braido[1]

[1]Allergy & Respiratory Disease Clinic, Ospedale S.Martino Genova, Genova, Italy; [2]University hospital, Department of Biostatistics, Nimes, France; BESPIM; [3]Department of Internal Diseases, Allergology and Clinical Immunology, Medical University of Silesia, Katowice, Poland; [4]Department of Child and Maternal Medicine, The Melloni University Hospital, Milan, Italy; [5]Department of Otorhinolaryngology, Academic Medical Center, Amsterdam, the Netherlands; [6]Erasmus Medical Center in Rotterdam, the Netherlands; [7]Environment and Health Unit, ARPA Sicilia and Institute of Biomedicine and Molecular Immunology (IBIM), Italian National Research Council (CNR), Palermo, Italy; [8]Pneumoallergology Unit, S. Orsola FBF Hospital, Brescia, Italy; [9]Department of Dermatology and Allergy, Allergie-Centrum-Charite/ECARF, Charité– Universitätsmedizin Berlin, Germany; [10]Faculty of Medicine, Institute of Pathophysiology, Coimbra University, Coimbra, Portugal; [11]Clinical Sciences, University of Parma, Parma, Italy; [12]Allergy Service, Verona Major Hospital, Verona, Italy; [13]Department of Immuno Allergology, Coimbra University Hospital, Coimbra, Portugal; [14]Department of Respiratory Medicine, Montpellier University and INSERM U780, Montpellier, France

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**Correspondence**
Ilaria Baiardini, Allergy & Respiratory Disease Clinic, Ospedale S.Martino, Pad. Maragliano, Largo Rosanna Benzi 10, 16132 Genova, Italy.

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## Abstract

The aim of this Global Allergy and Asthma European Network (GA$^2$LEN) consensus report is to provide recommendations for patient-reported outcomes (PROs) evaluation in clinical trials for allergic diseases, which constitute a global health problem in terms of physical, psychological economic and social impact. During the last 40 years, PROs have gained large consideration and use in the scientific community, to gain a better understanding of patients' subjective assessment with respect to elements concerning their health condition. They include all health-related reports coming from the patient, without involvement or interpretation by physician or others. PROs assessment should be performed by validated tools (disease-specific tools when available or generic ones) selected taking into account the aim of the study, the expected intervention effects and the determinant and confounding factors or patient-related factors which could influence PROs. Moreover, each tool should be used exclusively in the patient population following the authors' indications without modification and performing a cross-cultural validation if the tool must be used in a language that differs from the original. The result analysis also suggests that the relevance of PROs results in any interventional study should include a pre–post assessment providing information concerning statistical differences within or among groups, rates of response for the PROs and a minimal important difference for the population. The report underlines the importance of further investigation on some topics, such as the quality assessment of existing PROs tools, the definition of inclusion and exclusion criteria and a more extensive evaluation of the correlation between PROs, besides health-related quality of life, and clinical data.

**Abbreviations**
EMEA, European Medicines Agency; FDA, United States (US) Food and Drug Administration; HRLQ/HRQoL, health-related quality of life; MID, minimal important difference; PROs, patient-reported outcomes.

## Concept and definition of health-related quality of life (HRQoL or HRQL) and patient-reported outcomes (PROs)

During the last 40 years, clinicians and researchers have recognized the importance of considering the subjective dimension of diseases to have a more global and coherent vision about the patient and the effects of the whole health-care process. This development was driven by the clinical necessity to go beyond the limits of 'disease-centred medicine' and reaches the wider and more global perspective of 'patient-centred medicine'. As mentioned in the WHO Health Report (2008): 'people-centredness is not a luxury, it is a necessity' (1). People do not think about health only in terms of targets for disease control programmes, but also in terms of what they perceive, according to their beliefs and their particular situation in life.

There are several definitions of this impact on subjective experience. Some researchers are prone to emphasize health aspects (HRQL or HRQoL); however, nowadays, the expression PROs seems to be more used, because it focuses on the interest in the whole host of outcomes. Anyway, it cannot be forgotten that in a nonclinical setting, PROs could mean *Person-Reported Outcomes* (2). PROs include all health-related reports coming from the patient, without involvement or interpretation by physician or others, such as *symptoms*, *HRQL*, *illness perception*, *satisfaction* or *adherence to treatment* (3). *Health Outcome Assessment* has also been proposed to avoid specifying the respondent (1).

Patient-reported outcomes have recently gained large consideration and use in the scientific community, with the aim of gaining a better understanding of patient's subjective assessment with respect to elements concerning their health condition (4). PROs focus the attention only on the patient, because she or he is the only person authorized to provide information about the personal experience of the disease, treatment and care. Therefore, PROs provide information unavailable from other sources, such as laboratory measures, caregiver reports or physician's judgements that is crucial for predicting health outcomes and for establishing health policy.

Patient-reported outcomes must be evaluated by validated tools exploring the patients' perceptions related to outcome. Specifically developed instruments such as questionnaires, composite scores and visual analogue scale (VAS) are necessary to understand how the patients perceive and evaluate their disease experience and therapy effects (4).

Patient-reported outcomes are affected by disease-related aspects (e.g. severity, chronicity, treatment schedule) and patient-related factors (e.g. alexithymia, stress, coping, mood). Moreover, each PRO can be influenced by other PROs – e.g. the level of asthma control may influence the HRQoL (5).

Patient-reported outcomes evaluation is relevant in clinical, research, routine medical practice and regulatory processes. The United States (US) Food and Drug Administration (FDA) (6) and the European Medicines Agency (EMEA) (7) have recently focused on PROs evaluation. EMEA suggests that especially in nonlife-threatening chronic conditions, when two drugs show similar efficacy, the patient's evaluation provided by PROs could be useful in defining the drug to be recommended. Between 1999 and 2003, 34% of all evaluations submitted to EMEA for the registration of a new drug, also for the use in the paediatric age (8), included data on HRQL and other PROs, and this rate has been constantly increasing ever since (9).

Recently, Scoggins and Patrick (10) showed that 14% of all international trials registered between September 2004 and September 2007 included a PRO as an outcome.

## PROs in allergic diseases

Allergic diseases constitute a global health problem: they appear to be increasing in prevalence and account for significant morbidity and socioeconomic costs (11). On the basis of this evidence, they have been defined as one of the epidemics of the 21st century (12).

Health-related quality of life impairment has been well established for rhinitis, asthma (13), atopic dermatitis (14), urticaria (15) and food (16). Allergic diseases exert a considerable economic and social impact not only because they are highly prevalent in many parts of world but also because their presence interferes significantly with many aspects of daily life as a result of physical discomfort and impairment along with emotional distress (17, 18).

A growing number of clinical trials for allergic diseases include PROs assessment (19–25). The aim of this GA²LEN consensus report is to provide recommendations for PROs evaluation in clinical trials for allergic diseases.

## PROs as primary, co-primary or secondary outcome

Assessment of PROs is rarely the primary but rather a secondary outcome in clinical trials (26–28). In this case, the trials sample size is calculated based on the primary outcome, and the results for PROs as a secondary outcome should be carefully evaluated in terms of the relationship between the PROs and the sample size.

The development of clinical trials in which PROs are the primary or co-primary (29) outcome is recommended because appropriate tools are available.

## Selection of instruments for PROs assessment

- The assessment of PROs should be performed by validated tools selected according to the aim of the study.
  - In clinical trials, disease-specific tools (whenever available) should be preferred over generic tools. Specific questionnaires are more sensitive than generic ones when measuring changes in the same population before and after an intervention. When a specific tool is not available, its development is recommended. A PROs tool can be considered validated if the validation procedure has been followed (Appendix S1), and if this procedure and its results are published in a peer-reviewed journal.
  - However, because allergic disease can affect more than one organ simultaneously, some tools can be used for the assessment of different clinical features (30).

  - For HRQoL assessment, 'generic questionnaires' should be used when a specific tool is not available or for a comparison between two different populations of patients [e.g. rhinitis *vs* asthma patients (13)] or between patients and healthy subjects (31). In this case, 'disease- or symptom-specific questionnaires' may be used in association with generic tools or alone (32).
- In trials that assess specific effects of an intervention (e.g. effect on sleep, on pain…), the choice of a specific PROs tool, whenever available, should be made taking into account the expected intervention effects.
- When PROs evaluation is part of a trial, determinant and confounding factors influencing PROs should be considered.
- A Ga²len registry of the validated tools is available on its Web site (http://www.ga2len.net). In the registry, the researchers can find data useful for the choice of the suitable tool according to the aim of the study (Table 1).
- All PROs and patient-related factors influencing PROs should be assessed using validated tools if available (Appendix S2).
- If symptoms are assessed using symptom scores, information about the validity, reliability and responsiveness of the tool should be provided when available (33).
- The VAS is a technique used to measure subjective phenomena (34). It is considered a robust, sensitive and reproducible method for symptom assessment (35). However, the interaction between the behavioural tendencies of patients and the physical characteristics of the scale causes it to be nonlinear and prone to response bias (35–38). For this reason, an assessment is subjective, and these scales are more valuable when looking at changes within individuals and are less interesting for comparing across a group of individuals at 1 time point (15, 34, 38).

**Table 1** Health-related quality of life and patient-reported outcomes Ga²len registry

| Name of the tool |
|---|
| Acronym |
| Author |
| Bibliographic references of the original questionnaire |
| Target |
| Population |
| Administration |
| Original language |
| Existing translations |
| Numbers of items |
| Tool dimensions |
| Scaling of items |
| Scoring of items |
| List of items |
| Minimal important difference |
| Shortened versions |
| Performed trials |
| Copyright |
| Contact information |

- The use of composite-validated clinical assessment tools – e.g. Asthma Control Test (39) and Asthma Control Questionnaire (40) is useful in clinical trials and real life assessment. The development of such kind of tools in all allergic disorders is encouraged. However, tools that include clinical/functional measures (e.g. peak expiratory flow) beside PROs (e.g. symptoms) are not fully patient centred (41).
- The administration time of an instrument in a clinical trial should take into consideration the time frame it refers to (e.g. instruments that take into consideration what happened in the last 4 weeks are not suitable for short-term trials).
- The methods of trials should include the reason(s) for choosing the PROs instrument selected.

### Patient-reported bias

In open-labelled trials, patient-reporting bias is troublesome, because the most obvious setting in which bias may be introduced by the patient is self-reported assessment, which represents the basis of PROs. Many examples can be listed such as pain scales and quality of life (42). Some of the most plausible factors inducing biases are apprehension bias (e.g. increased blood pressure when the subject is apprehensive), obsequiousness bias (subjects may want to please investigator) and expectation bias (43).

### Sample size and population in PROs assessment

- At present, information on the minimal number of patients to be involved in a clinical trial is not available for each PROs tool. A power calculation should be based on tools' features and the estimation of the drop-out rate.
- Each tool is to be used exclusively in the patient population for which it was developed and validated (e.g. use of adults' tools in adolescents is not correct).

### Correct administration of tools

- The use of PROs tools should follow the authors' indications (e.g. no medical or caregiver filling-in, no phone interview, no mail delivery if not indicated).
- The tool cannot be modified (items, instructions and response items), and no item can be added or removed.
- When using a tool, it should be checked whether its use is regulated or limited by patent copyright or commercial fees.
- A PROs tool can only be used in a language that differs from the original after translation and back-translation, and a cross-cultural validation is performed (Appendix S3). A simple translation of the tool is not sufficient.

### PROs result analysis

- The used tool should be analysed according to its structure (e.g. factor scores, global score). The analysis

of isolated items or item combinations different from the factors defined in the validation process is not allowed.
- Each score must be calculated according to authors' instructions.
- Complete results (i.e. positive) scores must be reported. The negative, no change and the number of missing data and response rates should be provided.
- It is not allowed to extend the results from one population to other patients populations (e.g. different age group/demographical data, disease severity, duration of treatment, etc.).
- Patient-reported outcomes analyses and reporting in clinical trials should take into account and/or be adjusted for confounding/influencing factors. These factors should be declared in advance.
- The relevance of PROs results in any interventional study should include a pre–post assessment. The results should provide information concerning statistical differences within groups or among groups, rates of response for the PROs outcome and a minimal important difference (MID) (44) for the population. This is relevant, because a single MID value for a PRO instrument does not exist across all patient samples. The MID may be different according to population and context, and no single MID may be valid for all study applications which refer to a PROs tool (45). Because the sample size of the study can be calculated only through study power, type I error and the expected effects, and these elements can be assumed only by past experiences, the use of MID calculated on previous studies is recommended.

## Unexplored areas and suggested topics of investigation

- Existing tool should undergo widespread cross-cultural validation to allow for their use in large multicentre international trials. New tools that are developed should be simultaneously validated in different languages (46).
- Minimal important differences for specific populations and PROs tools should be established.
- Further quality assessment of existing PROs tools is needed.
- The development of clinical trials in which PROs are the primary outcome is recommended.
- The correlation among PROs, patient factors influencing PROs as well as the correlation among PROs themselves should be explored.
- The impact of doctor/patient communication on PROs needs investigations, because currently patients' and doctors' viewpoints on the quality of their relationship differ significantly (47).
- Instruments for symptoms assessment should be optimized through a validation process.
- Patients influencing PROs should be investigated as factors to be taken into account in inclusion and exclusion criteria definition.
- A more extensive evaluation of the correlation between PROs, besides HRQoL, and clinical data is needed.
- For the paediatric population, the extensive use of PROs and the development in the paediatric investigation plans (PIPs) should be strongly encouraged. PIPs were introduced by the European Commission to help ensure that medicines for children are included in the mainstream drug development process in Europe, rather than as an optional extra (48).

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Appendix S1.** Steps for PROs instrument validation.
**Appendix S2**. Examples of Patient-Reported Outcome (PRO) instruments and examples of Patient-Related Factors that influence PROs.
**Appendix S3.** Cross-cultural validation.
**Glossary.**

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