RSNN ANNUAL WORKSHOP 2022 REPORT

Patient preferences: towards a more structural incorporation in the regulatory pathway

Medicine regulators have the role to assess the benefits and risks of medicines in order to ensure that only those medicines that have proven efficacy and safety (positive benefit-risk balance) enter the market and are available for the population. Assessing this balance is, however, sometimes challenging due to the heterogeneity of these two elements. Since 1965 medicine medicine regulations have been evolving, aiming to provide harmonization and guidance for this assessment. However, these assessments still require certain value judgments, which translate as the importance (value) given to the observed drug effects. These values are difficult to quantify, and might vary from person to person and among stakeholders, and may ultimately also affect the regulators opinion of the benefit-risk balance of a drug.

The elicitation and inclusion of patient preferences in regulatory assessments can enable a better understanding of how patients, the ultimate users of drugs, value the benefits and risks of a drug. Patient preferences are informative to regulators from a lived experience perspective rather than a theorical one, and the implementation of patient preference studies can contribute to more informed regulatory decisions with a greater patient-centred rationale.

During the annual Regulatory Science Network Netherlands (RSNN) workshop, various stakeholders discussed the challenges and opportunities of incorporating patient preferences in a more structured way across the various phases of drug development and regulatory assessment. The workshop was held in person on 5 September 2022 at the Jaarbeurs conference center in Utrecht and could also be attended online via livestream. The chair of the workshop, Peter Mol (Professor of Drug Regulatory science at the University Medical Center Groningen, assessor at the Dutch Medicines Evaluation Board and European Medicines Agency (EMA), and RSNN co-chair), queried the public about the benefit-risk balance of a lipid-lowering agent and briefly presented the various patient involvement

initiatives, past and ongoing, at the EMA. The workshop included a balanced representation of several stakeholders relevant to the regulatory ecosystem, i.e., patient representatives, regulators, basic scientists, industry, and researchers in the field of patient preferences.
This report provides a summary of the main discussion points and most relevant outcomes from the workshop.

After the opening session, the program continued with the presentation of Cristina Guerrero Paez, director of the Breast Cancer organization Netherlands (Borstkanker vereniging). Cristina provided an overview of the organization, including their main tasks, goals, and strategies on how to involve patients in drug development. She highlighted the large number of patients willing to collaborate with regulators and industry to get access to wanted and needed drugs, and the added value of these collaborations. Francesco Pignatti, regulator at the EMA, followed by describing the differences in perspectives of regulators, clinicians, and patients with regard to drugs, and emphasized the value of having input on the explicit trade-offs that patients are willing to make and how these might be taken into account at the time of taking regulatory decisions. Subsequently, Stan van de Graaf, Head of the Tytgat Institute for Intestine and Liver Research at the Amsterdam University Medical Center, focused on the importance of patient preferences to steer research in a very early stage of drug development. He presented how he organises events where patients are also active participants. For instance, they invited patients with rare liver diseases to meet researchers, which built a better awareness of each other's needs and challenges. He described how a mutual understanding improves communication and aligns perspectives, and the added value for researchers to gain knowledge concerning outcomes truly relevant for patients with liver disease. The pharmaceutical industry perspective was shared by Cathelijne de Gram (Janssen), who highlighted the growing number of drug applications containing patient experience data. She also elaborated on the various types of patient experience data in these dossiers and the multiple upcoming and ongoing initiatives on patient engagement. Isabelle Huys (Professor of Regulatory Science at Katholieke Universiteit Leuven, EMA), Rosanne Janssens (Katholieke Universiteit Leuven), and Liese Barbier (Katholieke Universiteit Leuven) presented the role and impact in the field of patient preferences of obtaining the European

Medicines Agency qualification of the IMI PREFER framework. This framework elaborates about why, when, and how patient preferences studies can be used in drug development and evaluation.

The meeting continued with a panel discussion chaired by Sjaak Bot (Janssen, RSNN co-chair), where multiple questions from the audience were addressed. The questions included the topics of patient centricity, how to educate and stimulate other investigators about the importance of patient involvement, the heterogeneity among patients about when and how much they want to be involved in their treatment decisions, and how investigators ensure the inclusion of minorities in patient preference studies, among others. Finally, the audience was challenged with an interactive preference elicitation exercise conducted by Douwe Postmus (University Medical Center Groningen), Hans Hillege (University Medical Center Groningen, EMA), and Sonia Roldan (University Medical Center Groningen). During this exercise, participants were given some background information about Alzheimer's disease, and they were asked to imagine they were living with an early stage of the disease. Participants responded to a couple of questions about their maximum acceptable risk in exchange for delaying their disease progression. The results of the exercise, which showed heterogeneity on the maximum acceptable risk of the participants, were then discussed. The exercise gave interesting insights into the design, methodology, and applicability of patient preference studies.

Where are we with patient preference studies?

Patient preferences can be defined as the qualitative or quantitative assessments of specific alternatives or choices with regards to a treatment outcome or health situation, and they were recognised by the stakeholders in the room to be a valuable source of information in preference sensitive decisions. For example, patient preference studies provide evidence about which outcomes may be more relevant for patients or the trade-offs that patients would make between the given benefits and risks of a treatment.

Various clinical and regulatory documents provide advice and encourage the inclusion of patient preferences in clinical and regulatory assessments, such as the EMA's Qualification Opinion of PREFER (1), the EMA's Regulatory science strategy to 2025 published by the EMA (2), the ICH reflection paper on patient experience data (3), the guideline for devices of 2016 published by the USA Food and Drug administration (FDA) (4), and the guideline published by the American Diabetes Association in 2022 (5). During the workshop, the presenters shared examples where patient preference studies contributed to the regulatory decision making. However, they also highlighted that regulatory guidance about when and how to perform patient preferences studies and about how regulators will consider the findings during the regulatory assessment is still limited, and they highly encouraged the development of such guidance. To achieve this, collaboration between stakeholders seems essential, and examples of continued dialogue between stakeholders were mentioned, such as 'Engagement Framework: EMA and patients, consumers and their organisations', the 'Multi-stakeholder workshop: Patient experience data in medicines development and regulatory decision-making', held by the EMA, and the IMI PREFER project.

The IMI PREFER project provides currently the most complete framework guiding on the design, conduct, and analyses of patient preference studies. The project took over five years to complete, and resulted in multiple publications as well as the public qualification opinion of the IMI PREFER framework by the EMA. The framework provides key information about multiple aspects of preference studies: the importance of defining the study purpose, the value of a multidisciplinary team, the timing in which the study should be performed, and the impact of the study design and conduct. The speakers from the IMI PREFER team stressed the importance of including patients as members of the research team, rather than as occasional collaborators. Obtaining a qualification opinion for this framework has helped to enhance the regulatory acceptability of patient preference studies, provides a foundation for future research, and supports the development harmonised guidelines by, for example, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

Still, how to ultimately use the collected patient preferences data in benefit-risk assessment is not always clear. This was addressed during the interactive exercise, where an example of patient preference data complimenting observed data from a clinical trials was provided. This exemplification used the ADDIS application (Aggregated Data Drug Information System), whose purpose is to measure benefit-risk balance in a quantitative manner; the information of a patient preference study where, for instance, the patients' maximum acceptable risk or minimum benefits are evaluated, can be compared with the observed benefits and risks of the observed effects. The exercise showed quantitively how a treatment can result benefit-risk balance positive, or not, depending on the individuals' trade-offs, and emphasized, therefore, the role of patient preferences in decision making. The field of patient preferences is growing, but there are still challenges to overcome and opportunities to pursue to ultimately improve their current use and acceptability in the regulatory context.

What are the challenges, opportunities, and next steps for the implementation of patient preference studies?

The current scenario with regard to patient preferences shows that different stakeholders still face challenges with the design, conduct, analyses, and implementation of patient preference studies.

Certain aspects need consideration when designing and conducting patient preference studies, such as whether patients will find the aim of the study understandable and relevant, and how the results of the study may improve their quality of care or life, which will facilitate their participation. During the interactive exercise it was clear that it is frequently difficult to adapt clinical language and clinical outcomes to patient-friendly language and patient-relevant outcomes, but that it is a crucial step to be able to use this information in clinical and regulatory assessments. Other points to consider are the logistics and financial aspects of involving patients, for example, to compensate their time and travelling costs, finding an accessible location, an adequate duration of the meetings or studies to avoid or reduce fatigue, or the requirements to adhere to data privacy regulations, among other aspects.

Other challenges of patient preference studies are the lack of familiarity with the methodologies to elicit preferences, how to analyze the data, and how to interpret the findings. While the value of patient preferences studies is generally recognised, not everyone involved in drug development might have sufficient resources to invest in these new methodologies. Moreover, if it remains unclear how these studies should be conducted to be acceptable for regulators or how they will be used in regulatory assessments and decision making. Regulators agreed on the desire for clearer guidance, but did not agree with the lack of guidelines being the sole reason to delay the use of patient preference studies. Experience with marketing authorisation application dossiers containing patient preferences studies are essential to develop the guidelines. Regulators highlighted the value of collecting patients' experience information using methodologically complex or simpler studies, through quantitative or qualitative data, and from small or large groups, and emphasised that these studies should not burden or delay the regulatory process.

In addition to the progress in the field of patient preferences, the opportunities for growth and improvement were discussed during the workshop. The participants of the workshop agreed that patient preferences studies provide complementary data that contribute to enhancing the decision-making process and improving communication through a more patient-centered approach. They also agreed on the increased insights that patient preference studies provide, especially for preference sensitive decisions when a clear positive benefit-risk balance is not immediately obvious from a regulatory perspective. Examples cited during the workshop illustrated the heterogeneity among the preferences of patients, emphasizing that when including the patient perspective in regulatory assessment, the various and heterogeneous patients' needs have to be considered.

While participants in the workshop shared an interest in the use of patient preferences in regulatory decision making, patient preference studies are relatively new and the methods are not always well known in broader audiences. Therefore, the need to increase familiarity with these studies and to raise awareness of their impact was highlighted, as well as the benefits of early interaction among stakeholders. An early interaction between stakeholders

ensures that everybody has the same understanding about the purpose and role of the study, the population where to conduct it, or the relevant outcomes, for example. Ultimately, the different participants reminded the importance of educating other researchers, sponsors, and decision-makers about patient preference studies and towards drafting fit-for-purpose guidance for conducting and using patient preference studies in drug development and and regulatory decision-making.

The workshop concluded with some recommendations from the chair, who emphasized the need for early discussion with decision-makers and collaboration among stakeholders to optimise the use of patient preferences in drug development and evaluation. The RSNN annual workshop brought together many relevant stakeholders in the field of patient preferences, and the interaction and discussion needs to continue. Greater transparency, early dialogue and well-informed regulatory decisions are the way forward in regulatory science, which may be enhanced by including patient preferences in these decisions. Raising awareness and education of all stakeholders, and sharing experiences, challenges, and learnings will facilitate the design, conduct, and optimal use of these studies as well as the drafting of regulatory guidelines that support the better incorporation of patient preference studies in drug development and regulatory decision making.

References

1. European Medicines Agency. Qualification Opinion of IMI PREFER. 2022. EMADOC-1700519818-808373.

2. European Medicines Agency. EMA Regulatory Science to 2025. 2020. EMA/110706/2020.

3. ICH. Proposed ICH Guideline Work to Advance Patient Focused Drug Development. 2021.

4. US Food and Drug Administration. Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling. 2016.

5. Introduction: Standards of Medical Care in Diabetes—2022. American Diabetes Association. Diabetes Care, 2022, Vols. 45(Suppl. 1):S1–S2.