Annex 1 of the Grant Agreement - Description of Action (DoA)

Action Full Title: Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle

Action Acronym: PREFER

- Grant Agreement no.: 115966
- IMI2 Call topic: IMI2-2015-05, entitled ‘Patient perspective elicitation on benefits and risks of medicinal products, from development through the entire life cycle, to inform the decision-making process by Regulatory Authorities, and HTA bodies.’
- Name of the coordinating person: Hansson, Mats
- e-mail address: Mats.Hansson@crb.uu.se

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List of participants (abbreviated name)

<table>
<thead>
<tr>
<th>Participant No.</th>
<th>Participant organisation name</th>
<th>Country</th>
</tr>
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<tbody>
<tr>
<td>1 (Coordinator)</td>
<td>Uppsala University (UU)</td>
<td>Sweden</td>
</tr>
<tr>
<td>2</td>
<td>University Medical Centre, Utrecht (UMCU)</td>
<td>The Netherlands</td>
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<tr>
<td>3</td>
<td>Erasmus University Rotterdam (EUR)</td>
<td>The Netherlands</td>
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<td>4</td>
<td>University of Leuven (KUL)</td>
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<td>5</td>
<td>University of Birmingham (UB)</td>
<td>United Kingdom</td>
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<tr>
<td>6</td>
<td>Universitätsklinikum Erlangen (UKER)</td>
<td>Germany</td>
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<td>7</td>
<td>Institute of European Oncology, Milano (IEO)</td>
<td>Italy</td>
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<td>8</td>
<td>MindBytes (MB)</td>
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<td>9</td>
<td>Istituto Tumori, IRCCS-Bari (ITB)</td>
<td>Italy</td>
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<td>European Cancer Patients Coalition (ECPC)</td>
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<td>11</td>
<td>Steinbeisser Project Management UG (SPM)</td>
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<td>Newcastle University (UNEW)</td>
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<td>15 (Project leader)</td>
<td>Novartis (Novartis)</td>
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<td>International Alliance of Patient Organisations (IAPO)</td>
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1. EXCELLENCE

1.1 Objectives

1.1.1 Introduction

The Innovative Medicines Initiative (IMI) is Europe's largest public-private initiative aiming to speed the development of better and safer medicines for patients. IMI supports this aim through collaborative research projects and building networks of industrial and academic experts in order to boost European pharmaceutical innovation.

In the IMI 2 Joint Undertaking, IMI has defined in its Strategic Research Agenda health priorities to ensure the needs of patients are adequately addressed and, where appropriate, patient involvement is encouraged (IMI 5th call for proposal, IMI2/INT/2015-01343, p.3). Beyond the IMI agenda, there is increasing recognition of the importance of incorporating patient needs and perspectives into decision making and to provide more avenues for patient engagement. Patients have expressed interest in seeing the decision-making processes of the European Medicines Agency (EMA)/Committee for Medicinal Products for Human Use (CHMP) take patient considerations into even greater account, e.g., in appropriate design of pre- and post-approval studies and risk management plans. For benefit-risk assessments in particular, decisions should take into consideration not only patient preferences but also endpoints and outcomes that patients regard as relevant, preferred treatment options, impact of the disease, and willingness to accept trade-offs between favourable and unfavourable effects.

While stakeholders are in agreement regarding the high value of patient input, an appropriate structured approach, including a set of systematic methodologies and recommendations for their use, is needed for inclusion and engagement of patient perspectives during the development, approval, and post-approval phases. This approach should accommodate the requirements of both Regulatory Authorities and other stakeholders, such as health technology assessment (HTA) bodies and reimbursement agencies.

Patient engagement is considered by all stakeholders as important; however, it is acknowledged that complex questions remain in relation to the methods to elicitate patient preferences and how to integrate findings into decision making.

1.1.2 Overall aim

The main objective of the project is to strengthen patient-centric decision making throughout the life cycle of medicinal products (a term which, in the context of this proposal, also includes medical devices) by developing evidence-based recommendations to guide industry, Regulatory Authorities, HTA bodies, reimbursement agencies, academia, and health care professionals on how and when patient-preference studies should be performed and the results used to support and inform decision making.

PREFER builds upon the experiences and outcomes of previous projects and initiatives, e.g., from the Food and Drug Administration (FDA), EMA, previous IMI projects like Pharmacoepidemiological Research on Outcomes of Therapeutics (PROTECT) and European Patients Academy on Therapeutic Innovation (EUPATI), and Medical Device Innovation Consortium (MDIC). Compared to these initiatives, the PREFER consortium takes a broader approach, engaging multiple competences and perspectives from all stakeholders involved, and it is focused on performing case studies to inform final recommendations. The PREFER consortium consists of 16 industry partners and 17 academic and subject matter expert (SME) members, including patient organisations, an elaborated Scientific Advisory Board, Stakeholder Advisory Board, Ethics Advisory Board, and excellent representation from different Member States. The engagement of the stakeholders goes from advisory input toward project-specific activities in order to meet stakeholder needs to the greatest extent possible.

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2 The EMA announced initiatives to address the subject of patient preference elicitation (http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2015/01/WC500180646.pdf)

3 The IMI PROTECT project (http://protectbenefitrisk.eu/)

4 The IMI EUPATI project (www.patientacademy.eu/)

5 The Medical Device Innovation Consortium’s Patient-focused Benefit-Risk Framework (http://mdic.org/pbfr)
1.1.3 General and specific objectives
The PREFER consortium has the following objectives:

- To determine how patient preferences may support decision making across the medicinal product life cycle and to ascertain which patient-preference elicitation methods are most promising to inform benefit-risk decision making at different decision points in the drug life cycle for industry, Regulatory Authorities, HTA bodies, reimbursement agencies, health care professionals, and patients
  To this extent, the specific sub-objectives related to this objective are:
  o to identify the stages in the product life cycle where patient preferences on benefits and risks may provide added value for decision making
  o to identify and assess which methodologies are most suitable for eliciting patient preferences on benefits and risks at different decision points in the product life cycle
  o to determine the needs, expectations, and concerns of various stakeholders (patients, industry, Regulatory Authorities, HTA bodies, and reimbursement agencies) regarding the use of patient-preference information and methodologies for patient-preference elicitation.
  o to translate the stakeholder input into formal research questions that can be tested
  o to evaluate methodologies that measure preferences for their capacity to capture heterogeneity of preferences and variability among individual patient perspectives, having regard to how well-informed the preferences are as well as being representative of a wider population of patients
  o to identify the assessment criteria used at the decision points in the drug life cycle
  o to identify a set of candidate methodologies to take forward for evaluation (identifying and implementing any required adaptations) and the criteria to be used to assess the case studies
  o to define parameters for case and simulation assessment
  o to draft study synopses that contain the major design features of the case studies

- To design, execute, and evaluate case studies
  The specific sub-objectives related to this objective are:
  o to translate the research questions and study synopses into concrete study designs and protocols for the case studies
  o to support the operational aspects of conducting case studies
  o to conduct case studies with appropriate scientific rigor
  o to evaluate the outcomes of the case studies
  o to provide results and conclusions ready for translation into recommendations

- To generate recommendations on patient-preference elicitation to inform benefit-risk decision making throughout the product life cycle for industry, Regulatory Authorities, HTA bodies, and reimbursement agencies
  The specific sub-objectives related to this objective are:
  o to identify the needs and requirements regarding patient-preference data of different stakeholders making benefit-risk decisions throughout the life cycle of a medicinal product
  o to define when and how to include patient preferences to inform benefit-risk decision making by industry throughout the product life cycle
  o to describe methodologies and procedures suitable for patient involvement, acceptable to and useful for patients, industry, Regulatory Authorities, HTA bodies, and reimbursement agencies
  o to define when and how to include patient preferences to support assessment and decision making by Regulatory Authorities, HTA bodies, and reimbursement agencies
  o to develop recommendations on lay communication for patients and other relevant stakeholders

It is crucial for the overall outcome of the project to engage all stakeholders, since acceptance and use of the recommendations, both within the industry as well as in other organisations, will depend on the quality and reliability of the case study results.
1.2 Relation to the call topic text

With the planned overall aim and the general and specific objectives, the project fulfils all requirements of the call Topic: IMI2-2015-05-01, entitled ‘Patient perspective elicitation on benefits and risks of medicinal products, from development through the entire life cycle, to inform the decision-making process by Regulatory Authorities, and HTA bodies.’

The call text indicates what is currently missing in view of patient preferences. First, there is lack of ‘An understanding of when and under what circumstances patient perspective elicitation on benefits and risks of medicinal products is most valuable.’ The PREFER project starts from the consensus among stakeholders that in order to make accurate and well-informed policy decisions regarding medicinal products, patient preferences should be included. Patients’ views on the benefits and risks and when benefits may outweigh harms should be better incorporated in the entire life cycle of a medicinal product, from the early phases of development and approval to decisions about reimbursement and whether rare adverse reactions should imply a withdrawal of the product from the market. Such views or preferences are based on data regarding safety, efficacy, medical need, and available treatment alternatives.

Although some countries, e.g., United Kingdom (National Institute for Health and Care Excellence, NICE), include patients in assessment panels, patient preferences in general play a limited role in the later stage benefit-risk assessments conducted within companies or by Regulatory Authorities, HTA bodies, or reimbursement agencies. The PREFER project is a response to this situation and to the call. It addresses the need for ‘A process analysis to identify which stages of the drug development life cycle are most suitable for patient involvement’ and will investigate ‘the circumstances which are most suitable for patient input.’ This will culminate in recommendations that define ‘how and under what terms the results of patient preference studies could be incorporated.’

The call text indicates a lack of ‘understanding of how patient-perspective elicitation on benefits and risks can best be performed to inform decision-making processes.’ To address this need, during the PREFER project, preference-elicitation methods will be identified, characterised, and applied in several stages of drug development, i.e., in the early stages of identifying medical needs, in clinical testing, and to guide decisions on reimbursement. Qualitative methods will be used to identify attributes and personal profiles. Quantitative methods will be used to ask patients to make trade-offs between benefits, harms, and other features of drugs in realistic scenarios, e.g., gain in life expectancy and gain in quality of life against risk of adverse reactions. The ‘appraisal of methodologies feasible for use by relevant stakeholders’ will be investigated throughout the PREFER project, as well as ‘the evaluation of such methodologies for a wider group of patients.’

The call text indicates that there is a lack of ‘experience with applying methodology to collect patient preferences.’ The PREFER project plans to carry out several case studies adopting, in a structured way, selected patient-perspective elicitation methods, as well as an assessment of the case studies, in order to address this need. During the PREFER project, ‘scientific, regulatory, and legal limitations and biases and opportunities of such methodologies’ will be highlighted and addressed. The main strength of the PREFER project is the strong integration of the diverse work packages, which fosters expertise exchange and continuous dialogue about evolving issues. The call text finally indicates there are ‘widely divergent views between stakeholders on patient preferences (which) should be elicited.’ The PREFER consortium intends to create recommendations in close dialogue with all stakeholders by identifying and involving these stakeholders from the beginning with the PREFER project in diverse ways (in a Stakeholder Advisory Group or project-related tasks) and organizing expert panels and consultation rounds in order to formulate recommendations created by a common understanding of all stakeholders.

1.3 Concept and approach

The final goal of PREFER project is to establish recommendations with the view of supporting the development of guidelines for industry, Regulatory Authorities, and HTA bodies on how and when in the product life cycle to consider patient perspectives on benefits and risks of medicinal products to inform the decision-making process by Regulatory Authorities and HTA bodies. This objective will be met by activities outlined in the tasks addressing the major stakeholders (industry, Regulatory Authorities, HTA bodies, reimbursement agencies, and patients [including patient representatives, children, parents, and care givers]) throughout the whole medicinal product life cycle.

The lifecycle of a medicinal product (illustrated in Figure 1) covers several phases, from preclinical and clinical drug development to drug approval, market introduction and use, and reimbursement phases. The PREFER proposal, which addresses the entire drug life cycle, is multidisciplinary at its heart, with all partners committed to the following approach.
It is acknowledged here that patient preference is not a new discipline and a variety of approaches have been used in previous research, including IMI PROTECT. Although these and other studies have shown that the systematic collection of patient preferences can be accomplished, and at varying stages of development, patient involvement is still limited largely to the individual ‘patient testimonial,’ which is most conspicuous at scientific advisory meetings. Most importantly, patient-preference elicitation studies are not currently required to be submitted as part of regulatory approval and for reimbursement applications. Because of this, there is little guidance and practical experience on how the results of these studies can be incorporated into regulatory, HTA, and reimbursement decision making.

A current gap that the PREFER project will address is the identification of stages in the product life cycle where patient-preference elicitation studies might be of added value in regulatory, HTA, reimbursement, and other decision-making and an identification of the most appropriate methodologies in these stages. This is an important component of the project, since conducting patient-preference elicitation studies are often time-consuming, expensive, and may be burdensome to patients. Another current gap is the lack of information on how patient-preference elicitation is conducted in paediatric populations and how these studies need to be conducted in rare diseases. PREFER seeks to involve different patient populations, with acute and chronic diseases, and with more common as well as less common diseases.

How to incorporate patients’ preferences in decisions regarding the benefits and risks of a medicinal product during its life cycle will be cautiously and thoroughly investigated. As described in a comprehensive review of how to visualise benefits and risks in Work Package (WP) 5 of IMI PROTECT, one of the predecessor projects to this call, there is sufficient scientific evidence on how visual tools may ease the communication about risks. There are also considerable recent literature on shared decision making and patient’s decision aids (Barry MJ, 2012; Chakravarthy S, 2015; Coulter A, 2011. Eaton S, 2012; Minvielle, 2014; Pushparajah, 2015; Stacey D, 2014). However, a more open question is how to capture different attitudes and preferences of patients toward benefits and risks of medicines and how to assess the value of these preferences for regulatory decision making. Innovative medicinal product development and market access is not always a linear process as shown in Figure 1. Several issues, from methodological, demographic, and psychological points of view, will be considered in the PREFER project within the studies conducted to identify patient preferences.

Methodological issues: Apart from more strict methodological issues, e.g., the type of methodology providing preference, sample selection, framing effects, reliability, validity and biases, the heterogeneity in preferences across patients will be captured. This is of crucial importance because i) a drug may be approved for a subgroup of patients but not for the whole patient population, ii) some patients are willing to face larger risks of loss and accept more side effects than others, iii) some patients are in greater need of treatment than others, and iv) a parent and his/her child to be treated may have different preferences. Therefore, when measuring preferences, the target population should be carefully determined to guarantee that all stakeholder groups are represented and the study has sufficient power to determine possible differences among subgroups of the population.

Demographic issues: Differences in patients’ preferences are expected to be influenced by several demographic factors, including cultural background, age, gender, and socio-economic status. In addition, specific attention should be placed on health literacy as well as health numeracy. These concepts describe patients’ ability to access, understand, appraise, and apply health-related information in text and numbers, respectively. Patients with lower literacy and numeracy skills are known to have difficulties interpreting risk information correctly. Since the research interests within this application by definition incorporate risk information, patients’ literacy and numeracy are crucial to measure and take into account.

Psychological issues: The investigation of cognitive and psycho-emotional factors is crucial to understand and personalise different patient profiles in drug preferences and is a key concern in order to evaluate the representativity of elicited preferences.

Figure 1. Conceptual framework of the medicinal product life cycle

M.A. = marketing authorisation
preferences. A patient is a person with specific needs and values, habits and behaviours, hopes and fears, beliefs and cognitive differences, situational factors, decision style and decision competence. Generally speaking, benefit-risk perception is strictly dependent on how the human mind represents and processes incoming information so as to give rise to a whole predisposition toward specific items. A number of cognitive mechanisms have been described, generally known with the terms heuristics and biases. In particular, simple memory-based heuristics may modulate human judgment promoting specific decisions. Similarly, emotion may play a role in guiding judgment and behaviour. In assessing benefit-risk perceptions, all these effects and biases need to be well-characterised. Numerous observations in the field have shown that humans are characterised by a bounded rationality and that their decisions are often based on feelings and emotions which, whether naturally occurring or experimentally induced, exert a strong influence on individuals’ benefit-risk perceptions, benefit-risk preferences, and decision-making. Giving informational inputs into decision-making, emotions may influence individuals’ choices directly by evoking specific tendencies toward action and appraisal or indirectly by interfering with their ability to retain and process information, thereby impacting comprehension. In making decisions, people are forced to rely on simplifying cognitive short-cutting strategies (heuristics), which assist them in taking decisions especially when only incomplete or poor information is available. This perspective can be effectively used to evaluate patients’ preferences about benefits and risks of drug in its life cycle. In this context, patients’ predisposition on medication adherence and beliefs about medicines and drug attitudes will be investigated, as well as several variables concerning cultural and educational background, health locus of control and health-orientation personality style, optimistic bias and risk tolerance toward health, overconfidence in health conditions, and emotion regulation or dysregulation processes.

Assessment of preferences: There are also reasons for thinking cautiously of how to incorporate patients’ preferences as one of the elements of benefit-risk decision making. It might be argued that too narrow a focus on preferences neglects more objective elements in life that, arguably, have intrinsic value. It might be more objective to measure the health status of patients and the opportunities and performances for the individual patient such statuses enable. When patient preferences are elicited in order to guide policy and decision making, both Regulatory Authorities and patients themselves want to be appropriately informed. Preferences may also change due to deliberation. Decision makers along the line of drug development or at the point of market access (reimbursement), and in particular patients themselves, want their perspectives to be both appropriately weighted and assessed after some level of deliberation of the different values and concerns at stake in order to best guide policy and regulation.

Understanding of information in view of patient preferences: From an ethical perspective, understanding is a key issue, as highlighted by a recent preference study of patients with rheumatoid arthritis (RA). The study used conjoint analysis methodology to assess whether patient preferences differed by race in the United States (US). The study showed that African-Americans attached greater importance to the risk of toxicity and less importance to the likelihood of benefit than their white counterparts. The fact that preferences may be based on incomplete and inaccurate understanding and that this may be a source of racial disparity is discussed in the paper. Similar results were found in a study by members of the PREFER consortium. They studied to what extent health literacy and educational level are associated with parental preferences concerning childhood vaccination. Results showed that less-educated and less-health-literate respondents considered protection duration to be more important and vaccine effectiveness and frequency of severe side effects to be less important compared to more-educated and more-health-literate respondents. While all respondents were willing to vaccinate against rotavirus when the vaccine was offered as part of the National Immunization Program, only less-educated and less-health-literate parents were willing to vaccinate when the vaccine was offered on the free market. This heterogeneity in preferences is probably due to a lack of understanding or a misinterpretation, which caused respondents with a lower health literacy to neglect or otherwise undervalue specific information. These examples point at the need to examine not only what stated preferences patients express but also how well informed these preferences are. It is from this perspective that one should understand the introduction of educational tools such as serious games when eliciting preferences. The technological and methodological underpinnings of software game business have been laid down in years of research and development. They are now finding their way into non-entertainment contexts, helping deliver substantial benefits, particularly in education, training, research, and health. The SME MindBytes involved in the PREFER project has developed games with applications in several health areas to help empower patients and caregivers, enhance coping strategies, and capture patient profiles, behaviours, and preferences. It is known from previous work that attitudes to risk will affect preferences and one may embed questions/tests in the format of a serious game in a discrete choice experiment (DCE) to identify attitudes to risk.

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The PREFER project therefore aims at examining if patient preferences are related to how well informed patients are, e.g., through educational interventions. Here we want to explain the notion of well-informed preferences and their relation to educational interventions such as serious games and deliberative processes. A preference is understood as a person’s particular evaluation reflected in choice; a stated preference is reflected in a hypothetical choice, and a revealed preference is reflected in an actual choice. This general definition is in agreement with the MDIC framework. Preferences can be said to result from attitudes, understood as more general and basic evaluations, and relevant beliefs concerning the states of the world, actual or future. For example, if a patient prefers drug A over B, that preference might result from her negative attitude concerning a certain side effect and her belief that A causes less of such an effect than B. The truth of an empirical belief is difficult to determine with absolute certainty. Instead, we in science and elsewhere aim at well-founded beliefs and a belief is more or less well-grounded in the sense that it is based on and coherent with other beliefs.

When aiming at well-informed preferences, the aim should be to have well-grounded and relevant beliefs. For that reason, we propose to use elaborate educational tools such as serious games. Using such material can result in two kinds of preference changes:

- a desired change to more well-grounded beliefs and the formation of relevant beliefs (doxastic preference change). Relevant beliefs are beliefs of the patients having the preference about how they would experience different scenarios, i.e., beliefs from a subjective or narrative perspective of how it would be to have side effects.
- an undesired change to less well-grounded beliefs, deliberately imposed by a source of information that is not trusted (valuational preference change). This may be caused by biased information or other non-cognitive influences.

This results in the question of how educational interventions can be designed to cause doxastic rather than valuational preference changes. Plausibly through having the educational material, e.g., information, the scenarios of the games etc., to fulfill procedural criteria that should ensure trust. For instance by trying to make sure that information is not biased or one-sided e.g., on the selected attributes of a choice. This can be accomplished by letting different stakeholders with different perspectives, interests or values review and accept the information material to be used.

**Timing and requirements of preference elicitation methods:** The requirements for outcome measures regarding patient preferences might differ based on the phase in the medicinal product life cycle as well as product- and disease-specific characteristics. We propose to identify relevant preference-measuring methods per phase in the medicinal product life cycle, and most importantly to combine multiple methods to develop the most complete overview of patient preferences. Several methods can be thought of, which all can be placed among qualitative or quantitative research. Based on a comprehensive review of existing methods for elicitation of preferences of patients and the broad and excellent capability represented by cutting-edge experience within the combined multidisciplinary research team, including academic centers as well as industry partners, we will elaborate on a set of preference-elicitation methods within both the qualitative and quantitative research domains. The need to incorporate different views means that a robust and reproducible method of eliciting preferences for risk is needed. For the current application, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines of good-practice will be used as a starting point to reach optimal preference research. Questions about consistency and validity of results across different methodologies and national/cultural contexts are hereby key concerns.

**Consistency of outcomes:** The question of consistency of results depends on the type of methods being compared and their characteristics, always in relation to the case (and disease type) in which they are adopted. For some methods, convergent validity can be tested more easily than for other methods. To ensure the comparability of two methods, a within-sample comparison is recommended; for example, using a within-sample comparison between a DCE task and a direct-ranking exercise, we can determine to what extent the attribute importance score of a DCE is in agreement with a direct-ranking exercise. Additionally, using parametric and non-parametric tests, we can obtain insights into whether there are differences between methods in missing values, ease of task as perceived by the respondent, etc. A focus group will result in different outcomes than a DCE, but what information and outcomes are needed may differ per phase of the medicinal product life cycle. The methods chosen should be able to provide the specific information that is needed in that particular phase with that particular research question.

**Feasibility, reliability, and validity of the methods:** These aspects will be investigated alongside the aim to integrate the results into the decision-making process. It should here be observed that decision-making processes differ across countries, something that should be taken into account in the development of recommendations. Experience with the development of guidelines for the measurement of health-related quality of life (HRQoL) for relative effectiveness assessment in the context of the European Network for Health Technology Assessment (EUnetHTA) has shown that different systems have different
Development of recommendations: The project will deliver an overview of methods that are most appropriate to use within every phase of drug development and market access. This overview is part of a larger guideline which will describe in detail which method or combination of methods is most appropriate given any specific situation. Recommendations on the use of specific elicitation methods will be stratified not only based on the development phase but also regarding methodological issues as well as specific drug and patient characteristics (demographic and psychological issues). The feasibility of the recommended methods will be assessed both in terms of burden for the patients involved and costs.

Five-step strategic approach: In order to end up with a complete overview of methodological approaches together with additional practical recommendations, we propose to use a five-step research strategy for the PREFER project. A multidisciplinary approach will be used to end up with recommendations for industry, Regulatory Authorities, HTA bodies, and reimbursement agencies to measure and incorporate patient preferences within the medicinal product life cycle.

Step 1: Each step of the medicinal product life cycle will be identified with a catalogue of activities that are carried out in every phase and the type of decisions that have to be made. To do so, both literature research as well as interviews with the industry, Regulatory Authorities, HTA bodies, and reimbursement agencies will be conducted until data satisfaction. We will also identify the type of evidence gathered during the whole medicinal product life cycle as a basis for further discussions with stakeholders. The PREFER consortium includes partners with advanced knowledge about medicinal product development processes and market access procedures.

Step 2: Thereafter, it should be determined at which steps patients’ preferences are worthwhile to include given specific circumstances. This step will be completed by literature research as well as group discussions per stakeholder group, hence separately with patients, industry, Regulatory Authorities, HTA bodies, and reimbursement agencies.

Step 3: Available methods will be identified to measure preferences both qualitatively and quantitatively. This step will be undertaken by literature research as well as expert interviews with researchers specialised in either qualitative or quantitative methods to elicit preference methods until data satisfaction. Diverse partners have expertise in methods for preference determination. During the interviews, it will also be discussed for what specific purposes and in what specific circumstances every method is most appropriate.

Step 4: Based on literature and a discussion round with experts on preference elicitation until data satisfaction, criteria will be established to rank the identified preference-elicitation methods by usefulness within every step of the medicinal product life cycle. Based on those criteria, a first ranking of all identified methods under Step 2 will be conducted. Per case study (see description below), the most appropriate preference-elicitation method will be selected.

Step 5: Based on the results of all previous steps and in combination with focus-group interviews with patients and patient representatives, clinicians, experts from industry, Regulatory Authorities, HTA bodies, and reimbursement agencies, the recommendations will include:

- which qualitative and quantitative methods are most appropriate to use within every separate step in medicinal product development and market access phases
- which methods are most suitable given a specific target population
- which methods are most suitable given the specific characteristics of the medicinal product
- what are the educational approaches for involvement of patients into decision-making processes

1.3.1 Case studies

We will select the best available and developed method of preference elicitation for testing of clinical case studies in three disease areas: i) cancer, ii) rheumatology, and iii) neuromuscular disorders (NMD). In addition, several case studies will be conducted in association with already-planned drug development projects of the participating pharmaceutical companies. The case studies are selected in order to capture a wide variety of relevant preferences throughout Europe, including Central and Eastern Europe. The case studies are characterised by:

- diseases that are chronic, acute, life-threatening or debilitating, affecting functioning and daily activities;
- diseases whose frequencies are prevalent as well as very rare
- diseases affecting children as well as adults with a spectrum of severities and a spectrum of experiences with currently available treatments
- diseases for which there are currently no therapies or very few therapies
- diseases that have a severe impact on identifiable subpopulations such as children
d. diseases that may be targeted with medical therapy, prevention, or screening

The particular, case studies will be designed to accommodate not just development phase but also a broader relevant context: current information on benefits and risks; time available; budget; audience for the analysis; research questions being addressed; prior use of the methods in this context; ability of patients to participate in the case studies, regardless of the chosen method; and ability for output to inform recommendations applicable to industry, Regulatory Authorities, HTA bodies, and reimbursement agencies.

1.3.2 Input from related projects
The PREFER consortium represents a wide participation in finished and ongoing research projects focused at preference elicitation and medical risk communication:

a. Mind the Risk (Partners 1, 5, 7, 8) is a multi-disciplinary research program representing strong academic centres in Europe providing a rich philosophical and conceptual framework that together with historical and socio-cultural analyses of concerns about risk information, empirical investigations of risk perceptions and preferences, and ethical analyses, may guide regulation and management of risk information in various settings (www.crb uu.se/mind-the-risk/).

b. Partner KUL (Partner 4) is engaged in diverse projects relevant for the current IMI project: i) a study toward benefit-risk analysis methods in Europe and in the US: literature studies have been carried out to highlight diverse benefit-risk methods, i.e., quantitative methods (number needed to treat [NNT] and number needed to harm [NNH]) and qualitative methods. The study also covers the benefit-risk methodology project of EMA, the Unified Methodologies for Benefit-Risk Assessment (UMBRA) initiative of the Centre for Innovation in Regulatory Science (CIRS), and projects of ISPOR; ii) a study about societal preferences for the reimbursement of oncology drugs: a project studying societal preferences for characteristics of oncology drugs in a sample of 3,500 individuals in Flanders and the Walloon region. The study adopts a DCE; iii) a study about perspectives of patients towards non-reimbursement of drugs for overreactive bladder disorders; and iv) a study on the role of real-world evidence (RWE) in drug development as input for decision making (collaboration between Katholieke Universiteit Leuven, Vierick Leuven Gent Business School, Universiteit Gent, and the European Organisation for Research and Treatment of Cancer [EORTC]).

c. KCE (Partner 13) is studying: i) the acceptability and feasibility of citizen and patient involvement in health care policy, from defining overall priorities for health care policy to deciding about the reimbursement of specific products and services. Models for patient and citizen participation, supported by the stakeholders, have been developed based on a Delphi approach; ii) a project studying the relative importance of several reimbursement decision criteria according to the general Belgian public, using DCEs in >4,800 citizens; and iii) development of a methodology for assessing therapeutic and societal needs: an ongoing project aiming at developing a MCDA tool for the assessment and appraisal of therapeutic and societal needs. The tool incorporates public preferences obtained by means of DCEs and patient preferences obtained by means of participative qualitative techniques (diaries, focus groups, cards) (https://kce.fgov.be).

d. Euro-TEAM (Partners 4, 5, and 1) is conducting a project of the European Community’s 7th Framework Programme (FP7) for identification of biomarkers and disease mechanisms operating during the phases of disease leading up to the development of RA and translation of these findings into improved and user-appropriate acceptable diagnostic kits and strategies. One part includes work with users to develop and test strategies for the effective communication of issues related to risk stratification during the transition phases from heath to RA. Patient research partners (PRPs) have played a key role in the design, delivery and dissemination of a number of elements of this project (http://www.team-arthritis.eu/patient-research-partners.html) and several of these PRPs will support the current proposal in equivalent ways. E-com@eu, EMC (Partner 33) is conducting

e. E-com@eu, EMC (Partner 33) is conducting a project of the European Community’s FP7 (2012-2016) that aims to develop an evidence-based behavioural and communication strategy for health professionals and agencies throughout Europe in case of major outbreaks (http://www.ecomeu.info) by integrating social, behavioural, communication, and media sciences. Besides coordinating this multidisciplinary project, we developed and conducted 17 focus groups and four DCEs to investigate, quantify, and compare preferences of citizens from different parts of Europe for vaccination programmes during major outbreaks.

f. UMCU (Partner 2) studied willingness to participate in preventive interventions. Within their four-year project, five DCEs were conducted to determine the willingness of patients and the general population to participate in preventive interventions (i.e., lifestyle programs, rotavirus vaccination, and genetic screening for colorectal cancer). Besides these outcomes, several methodological themes within DCE studies were investigated.
1.3.3 Liaising with other EU projects or industry and regulatory initiatives

As mentioned in the call, the PREFER consortium will consider the activities performed in several ongoing European projects:

- The Advance HTA project (http://www.advance-hta.eu/), which aims in particular at improving the robustness of the evidence on the elicitation of preferences by deriving these in more realistic settings, by drawing on the wider European Union (EU) citizenship and from within the patient community

Synergies with academic institutions such as the Patient-Centered Outcomes Research Institute (PCORI), as indicated in the call text, will be defined and strengthened.

In addition, the PREFER project will consider the regulatory and industry initiatives as starting points for its respective work packages:

- FDA CDER’s Patient-Focused Drug Development
- FDA Center for Devices and Radiological Health’s (CDRH’s) Patient Preference Initiative
- MDIC’s Patient-Centered Benefit-Risk project
- Health Canada
- EMA’s pilot project on patient input for drug review
- Pharmaceutical Research and Manufacturers of America (PhRMA), the Biotechnology Industry Organization (BIO), and other pharmaceutical and patient group organisations’ detailed commentary to the FDA’s request for public comment on strategies to obtain the views of patients during the medicinal product development process and ways to consider patients’ perspectives during regulatory discussions

1.4 Ambition

Over the last decade, the patient voice has become heard more often in e.g. research granting bodies, institutional review boards, technology appraisal committees, regulatory and HTA body assessment panels. Although some pharmaceutical companies perform patient preference research alongside their registration studies, explicitly and deliberately taking account of patient preferences is uncommon along the medicinal product life cycle. For patient-preference studies that are used within the medicinal product life cycle, agreed standards on the design, conduct, analysis, and especially use of the findings in decision making are lacking. Importantly, industry, Regulatory Authorities, HTA bodies, and reimbursement agencies have key uncertainties regarding the validity, representativeness, and robustness of preference studies to inform deliberative decision making. What is currently missing is a shared understanding among all key stakeholders of (i) what constitutes a methodologically-sound patient-preference study; (ii) how the results from such a study can be incorporated in the decision-making processes of industry, Regulatory Authorities, HTA bodies, and reimbursement agencies; and (iii) at which stage(s) in the product development process and life cycle this information can best be collected. The recommendations that will be developed in the PREFER project will address each of these outstanding questions. Additionally, the outcomes of this project will result in increased understanding of patient preferences when it comes to new
medicinal products among industry, Regulatory Authorities, HTA bodies, and reimbursement agencies. Such insights will likely result in improved adaptation of medicinal products to patients' needs and wishes which in turn will benefit patient satisfaction and health outcomes.

The recommendations from PREFER project will be recognised, adopted, and used by a broad group of stakeholders. Similarly, patients will increase their understanding of the benefits and risks associated with their treatments, increase their confidence in determining the trade-offs of their treatments, gain knowledge to contribute to shared decision-making and give valuable insight to the industry, Regulatory Authorities, HTA bodies, and reimbursement agencies on their medical needs. In order to achieve this future state of the PREFER recommendations being broadly acknowledged, supported, and implemented, all relevant stakeholders will be involved in PREFER from the project's inception. Key stakeholders will play an active role via repeated consultations with the PREFER project team, which will be supplemented with an extensive communication plan in order to adjust for the information needs and decision-making processes of the various stakeholders.

The ambition of PREFER is to incorporate the use of patient preferences across the medicinal product life cycle and the strongest demonstration of the value of PREFER will come from its use by pharmaceutical companies, and its acceptance by Regulatory Authorities, HTA bodies, and reimbursement agencies. The ideal achievement of the PREFER project would be a global, harmonised approach to the use of patient-preference studies by industry, Regulatory Authorities, HTA bodies, and reimbursement agencies. The horizon after the PREFER project is a world where collecting patient preferences is as common as collecting information on adverse events and quality of life.

The ambition and innovation potential of PREFER is high. A broad array of (combinations of) patient preference methods will be tested prospectively in a large number of case studies. The availability of large patient cohorts will enable to test new methods or deviations from existing methods in a randomized manner, by comparing well-known methods with newer ones. The use of simulation studies will both contribute to smarter design of case studies and to exploring the sensitivity of outcomes of preference studies. Based on discussions with stakeholders, suitable methods will be tested and their contributions to improved decision making will be discussed in recommendations adapted to the needs of all relevant stakeholders. The recommendations from PREFER are expected to lead to changed practices, in that industry will routinely assess whether a preference study would add value at key decision points in the medicinal product life cycle and, if so, implement patient-preference elicitation studies according to the PREFER project recommendations. Patients and patient organisations will become more integrated into decision making at key decision points and develop closer partner relationships with the industry, Regulatory Authorities, HTA bodies, and reimbursement agencies. The regulatory, HTA, and reimbursement authorities will routinely include the patient's perspective and appropriate acknowledgement in their decision-making processes. The output will not only be used by these decision makers, but will also serve as an additional source of information to adjust or discontinue medicinal product development processes and inform health care providers and patients. Given the level of expertise and stakeholder involvement that will be leveraged during the conduct of the PREFER project, it is expected that a wealth of data will be generated via the case studies. Identification of subgroups of patients, the existence of cultural differences in preferences, requirements for conducting preference studies within the industry and other settings, and support for the communication of preferences for benefits and risks of medicinal products will enable the implementation of personalised medicine.
2. IMPACT

2.1 Expected impacts

Stakeholders involved in the development and life cycle management of medicinal products agree that greater patient involvement is needed to ensure patient preferences are identified and considered. But while stakeholders agree on the high value of this form of patient involvement, appropriate structured approaches and recommendations on their use is needed to more broadly and reliably utilise patient-preference information across drug development, regulatory review, HTA, and reimbursement.

2.1.1 Expected impacts on research and development (R&D), regulatory, HTA, and clinical and health care practice

Impact on R&D and regulatory practice: To be approved for marketing, a medicinal product must be found to be safe and effective for its intended use. However, the meaning of safe is not explicitly defined in the statutes or regulations that govern approval. Recognising that all medicinal products have the potential to cause adverse effects, the safety of a drug is assessed by determining whether its benefits outweigh its risks. This benefit-risk assessment is the basis of pre- and post-market industry and regulatory decision making. There is an emerging consensus among stakeholders that patients should have a direct voice in assessing benefit-risk across the life cycle. While patient perspectives are routinely solicited and incorporated throughout development, sponsors, Regulatory Authorities, and other stakeholders struggle with assessing the validity of the views, and asking the question of whether the perspectives are representative, and if representative, how much weight should be given to the information. Beyond that, guidance is needed on how preference information can be rationalised for use in deliberative decision making processes, as is the case during development, regulatory, HTA, and reimbursement reviews.

Recognising that patients have value trade-offs, risk tolerances, and other preferences that can be better formalised to answer these and related questions, PREFER will advance patient-centered drug development and market access by confirming when and how preferences are best incorporated into R&D, regulatory, HTA, and reimbursement review. With more productive patient/stakeholder participation, R&D, regulatory, and clinical and health providers can expect increased speed and personalisation of product development, clarification of population-based risk tolerances, decreased regulatory uncertainty, enhanced safe use, improved patient outcomes, and appropriately-priced products.

To achieve this level of impact, the PREFER project has cast a broad net and includes all relevant stakeholders, including patients, parents, and caregivers and their organisations such as the ECPC, MDUK, EPF, IAPO, and European Alliance of Patient Organisations of Rare Diseases (EURORDIS); 16 pharmaceutical companies; HTA bodies of different countries such as KCE (Belgium) and Canadian Agency for Drugs and Technologies in Health (CADTH, Canada); reimbursement bodies such as the National Institute for Health and Disability Insurance (NIHDI, Belgium) and the German Federal Joint Committee (G-BA); and Regulatory Authorities such as the EMA, the FDA, and the Swedish Medical Products Agency. Beyond preference elicitation, including methodologies for the consideration of patient profiles, effects of information and educational tools, as well as deliberation and ethical assessment (e.g., of how patients’ stated preferences should be balanced against cost-effectiveness, quality-adjusted life years, and medical need), PREFER will achieve a long-term impact by delivering a framework to change industry, regulatory, payer, and reimburser practices. Patient perspectives, elicited and assessed as described here, are vital instruments for the development of effective and safe products and, for each patient, improved and accepted drugs.

By involving patients, pharmaceutical companies, academia, Regulatory Authorities, HTA bodies, and reimbursement agencies in this project and by recommending methods and approaches to elicit patient preferences together, interactions among all parties will become stronger and remain beyond this project, and will stimulate further collaboration and academic research in the area of personalised medicine.

Impact on clinical and health care practice: An improved understanding of preferences is expected to deliver medicines preferred by patients who, in turn, are better prepared to discuss their preferences with their health care providers. Emphasising the prospects of improved understanding of benefit-risk preferences, it is expected that the PREFER project will improve clinical and health care practice by increasing practitioner awareness of risk tolerances and patient preferences, which can support an improved ability to match the right medicinal product to the right patient.
2.1.2 Strengthening competitiveness and industry leadership and addressing specific societal challenges

An improved ability to capture representative population-level patient-preference information should allow industry to address current gaps and challenges surrounding patient input and improve the ability to develop a deeper understanding of the benefit-risk preferences of patients, such as the endpoints of greatest importance to patients, the maximum acceptable risk/minimum required benefit for use in benefit-risk assessments, and the ability to understand differences in the preferences among stakeholders relevant to drug development.

At a broader level, the general objective of IMI2 is to better couple research and innovation through an emphasis on excellent science, industrial leadership, and tackling societal challenges. The goal is to ensure Europe produces world-class science, removes barriers to innovation, and makes it easier for the public and private sectors to work together in delivering innovation. To speed access, approval, and payment for more relevant and impactful outcomes for patients, PREFER responds to these priorities by connecting a pan-European network of industry members, academics, Regulatory Authorities, HTA bodies, reimbursement agencies, and patients to collaboratively support and perform innovative research on the high-priority topic of improved patient engagement and preference elicitation. The output of this collaboration, pragmatic recommendations to guide industry on the use of preference assessment in the development, regulatory, payer, and reimbursement context, will establish best practices, all necessary requirements for widespread adoption and use.

2.1.3 Improving European citizens’ health and well-being and contributions to IMI2 objectives

IMI2 aims to provide Europe with more efficient and effective medicines and treatments, to decrease public health care costs, and to strengthen the regulatory system. PREFER will contribute to each of these objectives by structuring the project to deliver recommendations on the use of patient preferences to inform benefit-risk assessment across the development life cycle of medicinal products. The recommendations are expected to help define and advance the science of patient input, and would include ways to overcome perceived and actual regulatory barriers to the use of preference information. A transparent understanding of regulatory requirements for the inclusion of patient preference information will decrease uncertainty for industry and, in combination with learnings gained regarding optimal timing and methods, lead to greater use of preference studies by industry. These improvements for regulatory authorities and industry should lead to a more efficient and effective use of medicines, with a subsequent reduction in public health care costs.

2.1.4 Barriers/obstacles and any framework conditions (such as regulations and standards) that may determine whether and to what extent the expected impacts will be achieved

Delivery of the expected impacts may be qualified by patient engagement-related factors, which may include as yet unknown and unidentified issues related to patient education and training, ineffective communication, and/or cultural and perception barriers. Additional legal and framework conditions related to regulatory and HTA reimbursement practice, which will be addressed in the context of the recommendations, include guidance on the use of patient preferences in the context of existing restrictions on the part of industry as to when and how industry is able to discuss product development, including benefits and risks, with patients.

2.2 Measures to maximise impact

The PREFER project will have impact on R&D, HTA, and regulatory practice by establishing scientific evidence-based best practices and delivering recommendations on the use of patient-preference methodologies to inform identification of medical need, benefit-risk assessment across the medicinal product development life cycle, and reimbursement strategies.

The PREFER project is an innovative approach to research how a patient's perspective on benefits and risks can be best be identified. The project will identify which stages of the medicinal product development life cycle are most suitable for patient involvement and of highest value to all stakeholders. The long-term impact of the project depends on how the results of patient-preference studies conducted by industry or academia can be incorporated into recommendations for industry, Regulatory Authorities, HTA bodies, and reimbursement agencies for their assessment of marketing authorisation applications or treatment reimbursement.

To maximise impact, stakeholders will be involved throughout the entire project, including the development and testing of preference-elicitation methods within clinical case studies. The close collaboration with stakeholders will ensure that the results are relevant, understandable, and available. This is expected to ultimately result in a high degree of acceptance of
the resulting recommendations by all stakeholders including decision makers at Regulatory Authorities, HTA bodies, and reimbursement agencies. The results from this project will be placed in the public domain via several outlets, including open-access publications, which will also ensure that the scientific impact is sustained beyond the life of this project.

2.2.1 Dissemination and exploitation of results

Our dissemination strategy (carried out by WP 1, Task 1.2) aims to share experiences and results, promote discussion, generate interest in the PREFER project, and encourage collaboration and sharing of best practices among international academic and industry researchers, Regulatory Authorities, HTA bodies, reimbursement agencies, and patient organisations (through whom we will also reach health care professionals, families, and care-givers). The aim is that results from the project are taken up by stakeholders (e.g. regulators), while at the same time research continues towards new results and outcomes. Routes for dissemination will include joint publications, conferences, and workshops, but also a PREFER newsletter, website, and social media (outlined as part of the communication strategy, 2.2.2).

The PREFER project will organise a number of open workshops and events and invite academic researchers, industry members, and other stakeholders. Currently, three such events are planned (Table 1.1).

Table 1.1: Open workshops for stakeholders

<table>
<thead>
<tr>
<th>Workshop topic</th>
<th>Timing and plan for the workshop</th>
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<tbody>
<tr>
<td>Workshop on preference elicitation</td>
<td>At the beginning of the project, PREFER will send out an open invitation to discuss the project and receive input (WP 1, Deliverable 1.5)</td>
</tr>
<tr>
<td>Workshop on preliminary results</td>
<td>Towards the end, the PREFER project will present and discuss preliminary results at a similar workshop to receive input before issuing final recommendations. (WP 1, Deliverable 1.8)</td>
</tr>
<tr>
<td>Final event: Presenting recommendations</td>
<td>At the end of the project, PREFER will arrange an event at the European Parliament in Brussels to promote PREFER recommendations to key stakeholders. This event will be coordinated by WP 1 with the aid of ECPC, who has extensive experience organising this type of event. (WP 1, Deliverable 1.10)</td>
</tr>
</tbody>
</table>

Potentially, depending on the nature of the results and the interest, a final event in Washington D.C. could be arranged to extend the reach outside Europe. Budget for such an event would have to be found from outside sources.

Our dissemination strategy includes open-access publications in peer-reviewed, English-language, high-impact journals. This is to ensure results are available for individuals and organizations who do not have, or cannot afford, access to subscriptions to scientific journals. All publications resulting from the project will acknowledge IMI and the PREFER project, according to IMI and specific PREFER communication guidelines. The PREFER project will use green open-access standards, with some key publications having gold open-access.

PREFER is a multi-disciplinary consortium. This gives us access to a number of platforms for research dissemination. PREFER partners will present their research at relevant scientific and industry professional organisation conferences and relevant stakeholder meetings. These activities will be tracked as part of the Key Performance Indicators of the project (as described in WP 1, Task 1.1, Project planning and tracking). We will also participate in stakeholder workshops and conferences and disseminate research through newsletters and websites (as outlined in 2.2.2, Communication activities). The consortium includes established networks with active participation in all parts of Europe through memberships of participating partners, e.g. ECPC, EPF, and EURORDIS, as well as in other parts of the world through IAPO in addition to the global networks represented by industry and academic partners.

All details will be described in a dissemination and communication plan, which will be established by WP 1 (Deliverable 1.4) (Table 1.2).
Table 1.2: Dissemination strategy for stakeholder groups

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<tr>
<th>Stakeholder group</th>
<th>Coordinator</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient organizations</td>
<td>ECPC through the Patient Advisory Group</td>
<td>ECPC, MDUK, EPF, IAPO and RA patients will create a Patient Advisory Group who will present results at international conferences for patients. The Patient Advisory Group will give tailor-made keynote presentations at meetings organised by large patient organisations, or other key initiatives, several of them taking place in Eastern Europe. Patient Advisory Group members will produce regular newsletters and enable dissemination in a patient-friendly language (translated from English to other EU languages when necessary). They will also include their existing networks of health care professionals, including the ECPC General Assembly (the largest gathering of patients in Europe).</td>
</tr>
<tr>
<td>HTA bodies and reimbursement agencies</td>
<td>KCE through the HTA Advisory Group</td>
<td>KCE will use one-on-one contacts with individual officers in HTA bodies and reimbursement agencies to provide information and ask for feedback. This strategy is expected to increase commitment and impact. They will also use the EUnetHTA website and newsletter and the HTA Europe LinkedIn group to disseminate information. KCE is also co-lead of a work package on tools and methodological guidance in joint action 3 of EUnetHTA. This means guidelines developed within the PREFER project could possibly be added to that set of tools and guidance, if the general assembly of EUnetHTA agrees. Toward the end of the project, KCE will also organise webinars, conference calls, and teleconferences.</td>
</tr>
<tr>
<td>Regulatory Authorities</td>
<td>Project Leaders and Coordinators together with EMA through the Regulatory Advisory Group</td>
<td>Dissemination to Regulatory Authorities in Europe and the US needs to be handled carefully to respect the integrity of the regulatory domain and ensure their independence. During the course of the project, they will be informed through the PREFER newsletter and receive invitations to project workshops. Regulatory authorities will also be invited to the final event and receive copies of the PREFER project recommendations. Their input is assured by EMA and FDA representation together with national Regulatory Authorities in the Regulatory Advisory Board.</td>
</tr>
</tbody>
</table>

**Measurements:** The communication and dissemination strategy includes measurements that will be described in detail in the communication plan (WP1, Task 1.2). Some of the outreach measures we will use to follow-up effectiveness of the communication and dissemination work are:

- Website traffic (using google analytics)
- Level of engagement (replies to e-mails sent on lists, comments and shares in social media, questions at events and contact forms online, conversations going viral).
- The extent of interest in the news and work we put out, measured by media attention, attendance at events, sign ups to social media outlets and newsletters, RSS feeds etc.

When the project starts showing results and towards the end, we will include one or two formal measurements of attitudes to the use of patient preference studies and awareness of the PREFER project’s work among the target audiences. This will be done together with Patient, HTA and Regulatory advisory groups and within industry. It could take the form of an online survey that is carried out at two points in time: The first in connection with (or after) the workshop on preliminary results, the second in connection with the final event where the PREFER project presents its recommendations.

All outreach measurements will be fed back to the communication and dissemination strategies. They will also be an important source of information for the design of the sustainability plan.

**Commercialisation**

The industry and academia are not planning to commercialise patient-preference methods explored during this project; the expectation is rather development of experience and acceptance of the use of patient-preference methodologies. However,
there is commercialisation potential regarding serious gaming that could be done by the SME MindBytes. This commercialisation potential includes:

- gaining know-how on building preference-elicitation functionalities into existing platforms and tools
- gaining clinical validation of gaming platforms, giving them a competitive advantage over other serious games developers
- exploring options regarding the use of serious games in drug development
- gaining visibility within their targeted client base (healthcare, public, and non-profit sectors)
- building different serious games-based health care tools after participating in the PREFER project

**Type of data generated:** The data produced and used during the PREFER project can be divided into three groups of decreasing confidentiality:

- datasets containing personal data
- datasets containing non-personal data
- public datasets

Only datasets containing non-personal data can be made public. No non-essential personal data will be collected by PREFER participants (see Section 5, Ethics, for details on handling of personal data).

Patient data will be generated and processed during the activities planned in WP 2, WP 3 and WP 4.

- **WP 2** will generate datasets containing literature reviews, recorded interviews, transcriptions of interviews, and review of reports in preference research
- **WP 3** will create datasets containing both aggregated and patient-level de-identified survey data of historical preference studies from industry, survey data and simulation data from PREFER case studies, aggregated data and de-identified patient-level data from prospective case studies from industry, in addition to literature reviews, recorded interviews, and transcribed interviews.
- **WP 4** will generate datasets containing literature reviews and data resulting from expert panel discussions and consultation rounds.

Appropriate strategies and recommendations will be put in place to ensure (personal) data protection and patient privacy.

**Data management and protection:** The management of data generated in the case studies, historical case studies, and simulation studies will be governed by the data management plan (DMP) (WP 1, Deliverables 1.3, 1.6 and 1.9, M6, M18, M60). The DMP will be openly available on the PREFER project website. It will cover data governance rules, addressing topics such as data availability, quality, consistency, and security. Policies will be defined for how data management will be organised and what infrastructures will be available, especially for the different types of data used during the course of the project. This is especially true for the data collected and processed in the WP 3 case studies. Consent forms will contain information on how personal data will be managed (see Section 5, Ethics self-assessment, handling of personal data). The plan will specify where the data are stored, who is able to access the data, and who owns the data. It will also specify the time period for which the data must be stored, define the standards for data collection and evaluation, and specify whether data are suitable for sharing. A basic premise in the DMP is that the methodologies to be evaluated in case studies are already publicly available. However, for case studies conducted as part of ongoing medicinal product development projects within industry, there may be proprietary and privacy concerns that will be acknowledged and agreements made with industry partners on data management. This will be stated in the DMP and is herein referred to as data generated in industry-led studies as opposed to data generated in academic-led studies.

Copies of datasets containing personal data in the possession of partners other than their owner must be destroyed at the end of the PREFER project. These data will be destroyed by their owners after a fixed period of time defined, based on the DMP and on the local data protection laws of the owner. Other non-public and public datasets may be stored indefinitely. An effort will be made to archive public datasets to ensure their long-term availability for future researchers.

**IMI PREFER** will especially ensure that

- details which personal and/or sensitive data will be collected are described and submit this to IMI before the collection of data
- copies of approvals for the collection of personal data by the Institutional Data Protection Officer / National Data Protection authority are submitted to IMI before the collection of data
- IMI PREFER obtains from each institution where data will be collected written approval for the technical procedures that will be used for data protection for the project. These procedures must demonstrate compliance of the data
protection processes with the present European legal frame. A copy of this approval will be submitted to IMI before the collection of data.

- detailed of the level of de-identification of the different source of data and how protection of personal data is assured and approved by an ethical board and provided to IMI before the use of data
- if personal and sensitive data will be processed and transferred between non-EU and EU countries, relevant authorizations are provided to IMI before the use of any personal/sensitive data not publicly available
- detailed information on dissemination of results in case of rare diseases is approved by the Ethical Committee and a copy of this approval is submitted to IMI before dissemination
- details of any planned exchanged or transfer of samples and personal data with non-EU countries together with appropriate authorizations are provided before transfer / exchange

**Management of research data:** The datasets containing survey data and recorded and transcribed interviews generated by the academic-led case studies are by definition to be regarded as personal data and require safe storage and handling in accordance with national and European regulatory frameworks. To ensure that consortium researchers can have access, UU will provide a data repository in the form of a research file-sharing area on one of their servers. This will be created in WP 1 (Task 1.1). Data curation and preservation will be outlined in the DMP (WP 1, Deliverable 1.3). Data collected in previous studies, either by industry or academia, will be stored locally and will be treated confidentially. Prior to making these data files available to PREFER, it will be ensured that all data are pseudonymised. These data, as well as data generated in industry-led case studies, will be managed as per the DMP and any agreements made with the contributing industry partners. Aggregated results of industry-led case studies and/or patient-level data can be made available via the PREFER consortium data repository where it does not conflict with industry need for protection of commercially sensitive data or infringe on intellectual property rights of the participating industry partner.

**Re-use of data generated in the PREFER project:** Scientific organisations all over the world are promoting a principle of open science and the sharing of research data and materials. By making data public, we can prevent duplicate research and make new combinations of data possible. We can also save both money and time. The PREFER-generated data will be a valuable asset for furthering research. As Swedish universities are public authorities, data stored at UU would be considered public (the principle of public access to official records) when secrecy does not apply (this will be described in the DMP from WP 1, Deliverable 1.3). This way, we will be able to make the data available to the scientific community. In view of personal data, the rules explained above apply.

**Ownership and access to key knowledge:** The Consortium Agreement regulates the ownership and access to key knowledge generated in the project. Each dataset that is or will be generated will have an owner responsible for its creation and/or management. Non-public datasets may be transferred from the owner to a receiver in order to carry out the activities of the project. Storage media which are not accessible from outside of the owner’s or the receiver’s local area network must be used for the long-term storage of non-public datasets. In addition, the storage facility (e.g., database or file system) must provide an access-control mechanism which restricts access to authorised individuals and a logging mechanism which records all interactions with the data. For datasets containing personal data, national and local data protection rules may require additional protective measures.

**Sustainability:** Dissemination and communication activities will extend beyond the five years of the project. This will be outlined in a sustainability plan (WP 1, Task 1.1, Deliverable 1.7).

**2.2.2 Communication activities**

We want to further strengthen the awareness and discussion of patient preferences in benefit-risk assessment during the medicinal product life cycle, not only among target audiences (stakeholders including Regulatory Authorities, HTA bodies, reimbursement agencies, and patient organisations; industry, and academia), but also among the public and society at large. The communication strategy complements the dissemination strategy, and stakeholder partners will play a key role in designing this communication and coordinating activities (see 2.2.1. Dissemination and exploitation of results).

The PREFER consortium will apply a dissemination and communication strategy (WP 1, Task 1.2) that justifies the funds and resources provided by IMI. We aim to:

- inform our target audiences about the benefits of the project and how it develops
- maximise impact by encouraging involvement and interaction with stakeholders (e.g. regulatory authorities, HTA bodies, reimbursement agencies, and patient organisations)
create awareness within industry, Regulatory Authorities, HTA bodies, and reimbursement agencies about patient-preference elicitation methods
communicate how IMI research funding helps people and societies and furthers the economy and well-being for European citizens
create awareness among the wider public
find the right communication strategy to balance the uptake of the results by the regulators or other stakeholders while keeping the potential in the project for further innovation

**External communication:** The aim of our external communication activities (carried out by WP 1, Task 1.2) enables us to disseminate results more widely, generate interest in the PREFER project, build networks, receive input, revise strategy, inform, and influence. Some measures to reach the scientific community, pharmaceutical industry, and stakeholders are already outlined under dissemination (2.2.1). External communication also involves participating in the public debate. The communication strategy adds value by popularising research results, making them available for a larger audience. This allows not only for cross-disciplinary communication, but also extends the reach of the research results beyond the scientific community by presenting research in the form of web news, newsletters, press releases, and other press contacts and activities.

The PREFER project will work with Patient, Regulatory, and HTA Advisory Groups (WP 1, Task 1.6-1.8) not only to raise awareness and disseminate results using their existing channels, but also to identify new means to reach patients, healthcare professionals, and society at large.

We define four broad target audiences for external communication: the scientific community, the pharmaceutical industry, stakeholder groups, and finally, public and society (Table 1.3).
Table 1.3. External communication strategy

<table>
<thead>
<tr>
<th>Aim</th>
<th>Tool</th>
<th>Description</th>
<th>Scientific Community</th>
<th>Pharma Industry</th>
<th>Stakeholder Groups</th>
<th>Public and Society</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raising awareness</td>
<td>Website</td>
<td>The PREFER website will have a .eu domain and ensure the project is visible. Information will be tailored to different target audiences.</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dissemination and communication of results to a wider audience</td>
<td>Newsletters</td>
<td>PREFER will issue a regular newsletter presenting concepts and results. We will also publicise activities in partner organization newsletters.</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Influence</td>
<td>Public relations</td>
<td>We will use press releases, contacts with science journalists, the web, and social media to extend our reach (for example, KCE will use LinkedIn groups to disseminate to HTA bodies and ECPC will provide information to their European media partners).</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Debate</td>
<td>PREFER partners will participate in the scientific and public debate.</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recognition and identification</td>
<td>Graphical identity</td>
<td>We will create a logotype and graphical identity, including guidelines for use and instructions on how to acknowledge PREFER and IMI.</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Acknowledgements</td>
<td>All communications will acknowledge IMI and the PREFER project (according to IMI and specific PREFER communication guidelines)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

**Internal communication:** Our internal communication strategy (carried out by WP 1, as part of Task 1.1, Project coordination and management) aims to allow efficient and transparent interactions within the consortium and to create efficient information and research data-sharing between and within the WPs and advisory boards. We will use a web-based secure tool for project management (e.g., ProjectPlace) to manage administrative information, store documents and reports, create timelines, and follow up on deliverables.

The PREFER project will create structures that support knowledge management and facilitate good working relationships and communication within the project. We will also create structures that help partners disseminate and communicate their results. The PREFER project will set up strategies for internal communication that are designed to ensure work packages communicate and align their work and that deliverables and reports are produced on time (Table 1.4).
### Table 1.4. Internal communication strategy

<table>
<thead>
<tr>
<th>Aim</th>
<th>Tool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facilitate good working relationships and communication</td>
<td>• Regular meetings</td>
</tr>
<tr>
<td></td>
<td>• E-mail lists</td>
</tr>
<tr>
<td></td>
<td>• Research file sharing area (data repository)</td>
</tr>
<tr>
<td>Communicate and align WP work and ensure deliverables and reports are produced on time</td>
<td>• Cloud-based tool, e.g., ProjectPlace (information repository)</td>
</tr>
<tr>
<td></td>
<td>• Regular meetings</td>
</tr>
<tr>
<td></td>
<td>• E-mail lists</td>
</tr>
<tr>
<td>Communicate and educate all interested WP members on the methodologies selected for testing in case studies</td>
<td>• Workshops</td>
</tr>
<tr>
<td></td>
<td>• Educational seminars</td>
</tr>
</tbody>
</table>
3. IMPLEMENTATION

3.1 Work plan: work packages, deliverables, and milestones

3.1.1 Overall structure of the work plan

The PREFER project structure includes four work packages which jointly address the challenges described in Section 1:

- WP 1 covers the tasks associated with overall project management, dissemination and communication activities.
- WP 2 will seek to understand stakeholder concerns around the use of patient-preference studies, make recommendations about the methodologies to be used in the case studies and define criteria for how the case studies will be assessed.
- WP 3 will design, execute and evaluate the case studies.
- WP 4 will draft recommendations that incorporate the lessons learned from the case studies.

Figure 2 shows the tasks and the relationship between the four Work Packages. More detail about the objectives, tasks and deliverables from each WP can be found in section 3.1.2.

Figure 2 Work Packages and their tasks
The work needed toward the various WPs will vary over the course of the project, as shown in Figure 3.

Figure 3: Relative contributions of work packages over the course of the PREFER project.
The timing of the different WPs and their components are shown in Figure 4.

### Figure 4: Timing of work packages and components

<table>
<thead>
<tr>
<th>Description</th>
<th>Tasks</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>WORK PACKAGE 1: PROJECT MANAGEMENT</td>
<td>TASK 1.1 Project coordination and management</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 1.2 Dissemination and communication</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 1.3 Project controlling</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 1.4 Contractual management</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 1.5 Resource management</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 1.6 Management of PREFER Patients’ Advisory Group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 1.7 Management of PREFER Regulatory Advisory Group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 1.8 Management of PREFER HTA Advisory Group</td>
<td></td>
</tr>
<tr>
<td>WORK PACKAGE 2: PATIENT PREFERENCE ELICITATION ISSUES AND APPROACHES</td>
<td>TASK 2.1 Identifying desires, expectations, concerns and requirements of stakeholders about methodologies for patient preference elicitation and their use in making well-informed decisions involving medical</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 2.2 Determine processes, conditions, contextual factors that influence unilateral role of PP studies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 2.3 Identification of assessment criteria used at decision points throughout the drug life-cycle</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 2.4 Identification of preference elicitation methods</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 2.5 Identify educational &amp; psychological feature methods</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 2.6 Characterize and appraise the methods</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 2.7 Identification candidate methodologies &amp; criteria to assess empirical case &amp; simulation studies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 2.8 Develop study synopses and preliminary research questions for empirical case studies and simulation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 2.9 Expert notes about methods in view of different disease areas</td>
<td></td>
</tr>
<tr>
<td>WORK PACKAGE 3: CASE STUDIES</td>
<td>TASK 3.1 Designing of research templates for the case studies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 3.2 Translate the preliminary research questions identified in WP2 to study designs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 3.3 Identifying and assessing historical case studies from industry experience</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 3.4 Identifying and supporting prospective case studies from industry partners</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 3.5 F Empirical case studies 1-3 and simulation studies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 3.6 Conducting additional case studies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 3.7 Assessment of case studies based on criteria from WP2 and cross-case assessment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 3.8 Exploration if and to what extent the findings of case studies can be translated to other disease areas</td>
<td></td>
</tr>
<tr>
<td>WORK PACKAGE 4: RECOMMENDATIONS</td>
<td>TASK 4.1 Define scope of recommendations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 4.2 Preparation of operational requirements and best practices for conducting of case studies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 4.3 Creating draft recommendations and testing these for</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 4.4 Refinement of draft recommendations and confirming scope</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TASK 4.5 Formulating final recommendations</td>
<td></td>
</tr>
</tbody>
</table>
3.1.2 Detailed work description broken down into Work Packages

Table 3.1a: Work Package description

Work Package 1: project management

<table>
<thead>
<tr>
<th>Work Package number</th>
<th>Start Date or Starting Event</th>
<th>M 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>WP title</td>
<td>Project management</td>
<td></td>
</tr>
<tr>
<td>Participant number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short name of participant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person-months per participant</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WP title</th>
<th>Start Date or Starting Event</th>
<th>M 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project management</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>SPM</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Lilly</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>ECPC</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Actelion</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Merck</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>KCE</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>EPF</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>KUL</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>MDUK</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>IAPO</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

Objectives

The objectives of WP 1 are to:

- ensure the proper overall management of the project in order to strengthen and support the participants to achieve the objectives, complete the milestones in time, and provide the deliverables (Tasks 1.1 and 1.4)
- manage the interactions of the project-relevant boards (Task 1.1)
- manage the strategic interactions of the consortium with key stakeholders (creation and oversight of Patient, Regulatory, and HTA Advisory Groups to raise awareness of the PREFER project, receive advice and consultation on general strategy and output, and translate this into implications for WPs (Tasks 1.1, 1.6-1.8).
- develop a sustainability plan (Task 1.1)
- ensure a timely dissemination of project results (Task 1.2), in particular the final PREFER recommendations
- set up an effective communication infrastructure and foster the integrative process within the consortium (Task 1.3)
- make sure that the consortium’s contractual duties are carried out. Advise and guide the participants to comply with the IMI regulations and their contractual and legal requirements. Abide by the “good practice” of resources management as presented in the Financial Guidelines (Tasks 1.4 and 1.5)

Description of work: Overall approach

The Project Management WP has two main components: 1. strategic project management and 2. operational project management.

The strategic aspects are led by the Project leader (Novartis), the Coordinator (UU) and their deputies (Eli Lilly, KUL) in close collaboration with the other Management Board members. The strategic aspects focus on project governance, steering and communication.

The operational aspects are led by Merck KGaA (co-lead: Actelion), UU and SPM in close collaboration with the key stakeholder partners in the consortium (KCE, ECPC).

We will employ a modern approach to dissemination, exploitation, and communication that enables us to interact with each other in the project and to promote research in a manner that truly shows the aim of the IMI programme. The communication and dissemination strategy will be revised regularly to meet the needs of the project and partners. We foresee that dissemination and communication activities will extend beyond the five years of the project and continue according to a sustainability plan.

Task 1.1: Project coordination and management (Lead: Novartis, UU. Contributors: Lilly, Merck, KUL, Actelion, SPM, M1-60)

Project governance & steering: The Management Board will ensure that the governance of the project will be established as described in Section 3.2 and in the Consortium Agreement.

The Management Board will remain up to date about project progress by communicating regularly with WP leads, coordinating inter-relationships/synergies, ensuring the overall project stays on track and is meeting key milestones, and
working with WP leads to identify solutions to any issues or roadblocks. Key performance indicators (KPIs) will be identified at the beginning of the project and tracked throughout the duration of the project (Deliverable 1.2) (Novartis, UU, KUL, Eli Lilly).

Project meetings: The scheduling and organisation of professional and efficient project meetings and workshops belongs to the scope of tasks of the management team at SPM. Each of the meetings (General Assembly Meetings, Steering Committee Meetings every two months, Ethics Advisory Board, Scientific Advisory Board, Stakeholder Advisory Board and Stakeholder Network, Management Board, and WP 1 meetings) will be planned carefully in accordance to the respective meeting’s objectives (SPM).

Information repository: We will set up a secure repository for project management-related documents, including member lists of the consortium, meeting minutes, WPs, scientific and ethics advisory board, stakeholder advisory board and network with contact details, and other project-related information, using a web-based secure tool for project management (e.g., ProjectPlace). The consortium contact list will be generated and maintained by SPM. This tool combines functionalities for central document sharing with version control and can be used to track communication and feedback from, e.g., stakeholders. The tool will be populated with data from the Technical Annex and information subsequently generated in the course of the project, e.g., minutes or reporting-related documentation. All participants will have access to this tool (see Milestone 1) (UU and SPM).

Data repository: to ensure that consortium researchers can have access, UU will provide a data repository in the form of a research file-sharing area on a server hosted by UU. Access to the server will be managed by UU’s information technology division. The solution is hosted in secure facilities to which only a handful of system administrators with signed confidentiality agreements have access. Access to data will require creating a user account at UU. This means individuals have to provide proof of identity (identification documents and residential address) before entering the domain. Communications with the server will be encrypted. This solution ensures the data be curated and preserved according to Swedish legislation and European regulatory frameworks (e.g., Personal Data Directive (95/46/EC). The general rule is that data are preserved for 10 years after the project ends. At this point, a decision will be made whether or not to continue preserving it. This decision will depend on whether it still holds research interest. Further details on which data will be shared in the UU data repository, and which data might be shared via a different route, will be described in the DMP.

Data management: A Data Management Plan (DMP), outlined in 2.2.1, will be established to show handling of project data. The plan will cover project management data, research data, and data handling to support data sharing during the project, as well as to foster sustainability after the end of the project (Deliverables 1.3, 1.6, 1.9) (Actelion, UU, KUL, Novartis).

Sustainability plan: A sustainability plan shall be established to ensure the continuation of the work after the end of the funding of the project (Deliverable 1.7) (Novartis, UU, Eli Lilly, KUL, Merck).

Task 1.2: Dissemination and communication (Lead: UU. Contributor: Novartis, Lilly, KUL, Merck, ECPC, KCE, EPF, IAPO, MDUK km 01-60)
To have the intended impact, PREFER needs an extensive dissemination and communication strategy (outlined in Sections 2.2.1 and 2.2.2). To ensure an efficient internal and external communication, the dissemination and communication will acknowledge IMI and PREFER partners in a consistent way. The planning and coordination of these activities will be described in a dissemination and communication plan (see Deliverable 1.4). This plan will refer to the IMI communication guidelines and establish PREFER communication guidelines (e.g., use of PREFER logotype, review and approval process). It will be a solid project plan with defined activities, responsibilities, and timelines, including process for regular review and update. This includes launching a project website (Deliverable 1.1).

The dissemination and communication strategies define strategies for stakeholder involvement and outreach (2.2.1), with ECPC coordinating for patient organisations and health care professionals through the Patient Advisory Group (Task 1.6) and KCE coordinating for HTA bodies and reimbursement agencies through the HTA Advisory Group (Task 1.8). This includes arranging two workshops (Deliverables 1.5 and 1.8) and a final event in Brussels (Deliverable 1.10). A communication manager (UU) has been assigned within WP 1 and will be responsible for leading the planning and implementation of the communication and dissemination strategy in close collaboration with the Management Board and
Steering Committee. The communication manager is also responsible for setting up monitoring systems to track the outreach measurements defined in the communication and dissemination plan.

**Task 1.3: Project controlling** (SPM, M 1-60)
Deliverable reports will be assembled by the WP leads with the assistance of SPM and the compiled report reviewed by the Project Leader and Coordinator. These deliverables will be reported in detail during scientific meetings in PREFER. On a monthly basis, SPM together with the Management Board will monitor the overall progress regarding milestones and deliverables. Whenever necessary, the Management Board will assist the partners in achieving their goals. By compiling all information, checking numbers and documents, SPM will support the consortium in generating the yearly Project Periodic Reports according to the reporting guidelines, which will then be submitted to the IMI by the Coordinator on time.

**Task 1.4: Contractual management** (SPM, M 1-60)
SPM's principal task will be to assist the Project Leader and Coordinator in monitoring the compliance of the project with the IMI provisions (Grant Agreement and its annexes) and the Consortium Agreement. Therefore, partners will be trained on IMI provisions whenever relevant.

The Project Leader and Coordinator will ensure that the consortium complies with the rules on decision making in PREFER as defined in the Consortium Agreement. These procedures will be carefully followed when it comes to decisions on the implementation of work, funding, and other decisions on crucial issues. (For decision making mechanisms, see Section 3.2).

**Task 1.5: Resources management** (SPM, M 1-60)
SPM will assist the Project Leader and Coordinator with the collection and preparation of all cost reports (e.g., management report, report on the distribution of funds, Form Cs, and audit certificates) from the participants, which will then be submitted to IMI by the Coordinator.

The planning of subsequent periods, budget and expenditures need to be monitored, also new budgets must be calculated and be filled in the respective forms.

The Coordinator will, together with SPM, ensure that correct payments are being made to the partners.

**Task 1.6: Management of Patient Advisory Group** (Lead: ECPC. Contributors: EPF, MDUK, IAPO, M 1-60)
The PREFER consortium includes four patient organisation partners: ECPC, MDUK, EPF, and IAPO. Furthermore, a number of individual RA patients are involved through UB. These partners play a significant role, making sure the patient perspective is upheld at all levels in the PREFER project. Their perspective is complemented by the participation of EURORDIS on the Stakeholder Advisory Board. Together, they will create a Patient Advisory Group including representatives from other European and national organisations (according to the needs of the Patient Advisory Group). ECPC will be responsible for the coordination and management of the Patient Advisory Group.

The Patient Advisory Group will participate in the dissemination and communication (Task 1.2) activities in WP 1. This includes dissemination through member organisations’ newsletters, participation in conferences, and giving keynotes at meetings organised by large patient organisations (see 2.2.1, dissemination). As ECPC and EPF are based in Brussels, the Patient Advisory Group will play an important role in the organisation and execution of a final event in Brussels (see Task 1.2, dissemination, Deliverable 1.10). The Patient Advisory Group complements the patient organisation partners’ direct involvement in WP 2, WP 3, and WP 4 and allows for involvement of third parties. The Patient Advisory Group will organise five meetings in connection with the PREFER Annual Meeting and five teleconferences to substantiate patients’ input to the project. WP leaders can submit topic for discussion to the Patient Advisory Group ahead of their meetings.

**Task 1.7: Management of Regulatory Advisory Group** (Lead: EMA⁴, Contributor: Merck, Novartis, UU, M 1-60)
EMA will be responsible for the coordination and management of the regulatory stakeholder activities which will be consolidated in the Regulatory Advisory Group.

⁴ EMA is a external collaborator but no official beneficiary of the PREFER project
EMA will coordinate regulatory Stakeholder Board members (Swedish Medical Products Agency, FDA CBER, and additional representatives from EMA) and potential additional Stakeholder Network members.

The Regulatory Advisory Group will provide advice and consultation to the WPs and document this in meeting minutes and reports (see Section 3.2). The communication between EMA and the consortium will be facilitated by the project leader (Novartis) and the coordinator (UU).

Task 1.8: Management of HTA Advisory Group (KCE, M1-60)
KCE will be responsible for the coordination and management of the HTA body and reimbursement stakeholder activities which are consolidated in the HTA Advisory Group.

The HTA-AG will provide advice and consultation to the WPs and document this in meeting minutes and reports (see Section 3.2) and participate in the dissemination and communication activities as described in Section 2.2a in WP 1 (Task 1.2). These will be described in the dissemination and communication plan.

Deliverables (brief description and project month of delivery)
D1.1 – Website launch (UU, DEC, PU, M3)
D1.2 – Defining Key Performance Indicators (KPIs) (Merck, UU, KUL, Actelion, Novartis SPM, R, PU, M6)
D1.3 – Initial Data management plan (Actelion, UU, KUL, Novartis, R, PU, M6)
D1.4 – Dissemination and communication plan (UU, Novartis, Eli Lilly, KUL, Merck, ECPC, KCE, R, PU, M6)
D1.5 – Open workshop on preference elicitation (UU, Novartis, Eli Lilly, KUL, Merck, SPM, ECPC, KCE, DEC, PU, M12)
D1.6 – Update Data management plan (Actelion, UU, KUL, Novartis, R, CO, M18)
D1.7 - Sustainability plan (Novartis, UU, Eli Lilly, KUL, Merck R, PU, M48)
D1.8 - Workshop on preliminary results (UU, Novartis, Eli Lilly, KUL, Merck, SPM, ECPC, KCE, DEC, PU, M48)
D1.9 – Final Data management plan (Actelion, UU, KUL, Novartis, R, PU, M60)
D1.10 – Final event in Brussels (UU, Novartis, Eli Lilly, KUL, Merck, ECPC, KCE, SPM, DEC, PU, M60)
**Work Package 2: Patient preference elicitation issues and approaches**

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**Objectives**

The general objectives of WP 2 are to:

- determine the key topics and concerns that stakeholders (industry, Regulatory Authorities, HTA bodies, reimbursement agencies, patients, caregivers, and clinicians) have on the collection and use of patient preferences in the medicinal product life cycle and to obtain insight into which patient-preference elicitation methods are most promising to inform benefit-risk decision making for industry, Regulatory Authorities, HTA bodies, and reimbursement agencies at different decision points in the drug life-cycle
- provide timely input and recommendations to WP 3 on the design and goals of the case studies and to WP 4 on the translation of case study findings to recommendations for patient-preference elicitation

The specific objectives of WP 2 are to:

- determine the **desires, expectations, concerns, and requirements** of the various stakeholders (industry, Regulatory Authorities, HTA bodies, reimbursement agencies, patients, caregivers, and clinicians) about the timing and use of patient preferences and methodologies for patient-preference elicitation to support making well-informed decisions regarding medicinal products (Task 2.1)
- determine the **processes, conditions, and contextual factors** that influence patient-preference studies through a review and critical appraisal of available patient-preference research methodologies (Task 2.2)
- to identify the **assessment criteria used by different stakeholders** at the decision points in the medicinal product life cycle (Task 2.3)
- identify a set of candidate methodologies, both preference and educational/psychological, to go forward for testing and the criteria to be used to assess the case studies (Tasks 2.4, 2.5, 2.6, and 2.7)
- to develop study synopses and preliminary research questions for empirical case studies and simulation (task 2.8)
- give expert notes about selection and use of patient-preference methods throughout the product life cycle for final recommendations (Tasks 2.9 and 2.10)

This WP will identify the key topics and concerns that stakeholders have on the collection and use of patient preferences in the product life cycle and generate a complete overview of which patient-preference elicitation methods are most promising to inform benefit-risk decision making at different decision points in the product life cycle. The outcomes of WP 2 are reports and recommendations that serve as input for the case studies (WP 3) and the basis of developing valuable and reliable recommendations (WP 4).
**Description of work: Overall approach**

The use of patient preferences to inform decision making along the medicinal product life cycle triggers a diversity of questions by different stakeholders. Decision factors that may be considered include the decision context, including unmet medical need and treatment options available; the phase of product development; the decision point for which preference information is required; or other factors and conditions such as current information on benefits and risks, the nature of the benefits and risks, time available, budget, type of stakeholder in need of such preference input, type of patient-preference information required, whose preferences are assessed, the type of methodology that fits in a particular situation, and other topics yet to be identified. The WP 2 team will use a multi-step research strategy with both qualitative and quantitative approaches to generate a complete understanding of stakeholders’ key topics, concerns, questions, and requirements regarding the collection and use of patient-preferences methodologies. The work involves nine tasks:

**Task 2.1 Identifying desires, expectations, concerns, and requirements of stakeholders about methodologies for patient-preference elicitation and their use in making well-informed decisions regarding medicinal products via in-depth interviews** (Co-lead: KUL + UU + Takeda + CSL; Participants: EUR, IEO, IAPo, KCE, Actelion, JANSSEN, UNEW, Novartis, Pfizer, with the Stakeholder Advisory Groups). (M1-13)

The task has three steps:

1. To perform a literature study to develop initial assessment of desires, expectations, concerns, and requirements of stakeholders about the collection, use, and methodologies for patient-preference elicitation to support making well-informed decisions regarding medicinal products, until saturation has been reached.

   **Strategy:** First, a list of search terms and conditions will be constructed which will be used to identify the scientific literature and industry documents that will be in- and excluded from this review. Search terms to cover topics relevant for task 4.2 (operational requirements) will be included. Second, a formal literature search will be conducted in scientific literature using several search machines including PubMed and Medline, trade press reports/articles (e.g. BioCentury, PhRMA, EFPIA), patient advocacy group reports/articles (e.g. National Health Council, Faster Cures, Patent Project Muscular Dystrophy, Juvenile Diabetes Research Foundation), regulatory documents (e.g. marketing authorisation applications), and New Drug Application submissions and Regulatory Authority reviews. All information gathered will be combined in a structured overview which indicates the requirements, expectations, desires and concerns of stakeholders about the collection, use, and methodologies for patient-preference elicitation to support making well-informed decisions regarding medicinal products. This will result in a list of themes or topics that will form the basis for the interview guides that will be developed for the focus group interviews with all stakeholders. A report from this literature study will be used as a start in Task 4.1 and Task 4.2.

2. To perform focus-group discussions (FGD) with stakeholders in the Patient Advisory Group, Regulatory Advisory Group, and the HTA Advisory group, as well as with physicians, industry, and academic experts; these will be organised as several small (6-8 people) interactive group discussions on a short timeline to get results relatively quickly. These discussions will form the basis for in-depth, semi-structured interviews with all stakeholders.

   **Strategy:**

   At the start of the FGD research, the team will gather and an instruction session for all team members on FGD approach will be organized. Written consent will be obtained from all participants; FGD will be recorded and transcribed verbatim using a transcription protocol.

   Different FGD protocols will be designed for the different types of stakeholder if appropriate, each including a focus group guide as well as information about logistics, space required and scheduling of the FGD. FGD will be conducted in different countries representing different systems (in terms of decision-making about health care and economic approaches. Consequently, the protocols may be translated into different languages. The number of focus group discussions will be identified during the planning phase for this task.

   The focus group guide will ensure that all relevant questions are addressed and the participant discussions are conducted in a systematic manner. The content of this guide will be based on the themes and topics that are listed in step 1 (literature review).
Each of the focus groups will focus on at least 2 areas:

1. Legal/policy questions will address the impact on preference assessment of topics such as patient-industry relationships, the role of patients with industry connections, concerns about pre-approval discussions, the perception and potential of product/off-label marketing, the impact of who initiates and funds the elicitation of patient preferences, ethical considerations for decisions based on preferences, and the perception of industry bias. The final selection of topics will be adjusted to align with the outcome of the literature review.

2. Methodological questions will address topics such as formal assessments of sample selection and size, methodology selection, attribute/endpoint selection and completeness, validity, consistency/reliability, potential for roles of preference information in the medicinal product life cycle, patient and stakeholder heterogeneity, how well patients can perform these surveys, stated versus revealed choices, and suggestions for regulatory requirements for preference studies. As above, the final selection of topics will be adjusted to align with the outcome of the literature review.

All partners (industry and academic) of this task will be asked to identify as many experts as possible in their professional network (academics, physicians and industry members) regarding patients’ preferences and medicinal product development decision making. A random sub selection of all the individuals on this list as well as all members from the above mentioned stakeholder groups will receive an invitation to participate in a focus group. This selection will be based on country of residence.

Data will be gathered until data saturation as explained in Namey et al (American Journal of Evaluation, 2016). In general, thematic saturation is defined as the number of data collection events necessary to reach a point where little or no new information on the research topic emerges (Guest, Bunce, & Johnson, 2006; Guest, MacQueen, & Namey, 2012).

After data saturation has been reached, at least one member of each stakeholder group will be consulted again to evaluate if no important topics were missed. After this meeting either additional focus groups will be planned or the focus group phase is officially ended.

The intent is that the coding process will be conducted by the same team members in order to minimize variability (and enhancing comparability) across the data collections.

A report from these focus group discussions will be used as input for Task 4.2.

3. To conduct in-depth, semi-structured interviews with all the stakeholders until saturation has been reached. Interviews will include both the disease areas/patient organisations participating in the predefined case studies and other disease/patient stakeholders.

Strategy: Based on the list of stakeholders that was collected in the previous step, all people who did not receive an invitation to the focus groups or who declined focus group participation will be invited for an in-depth interview. This will, again, be based on country of residence.

The outcomes of the focus groups will be used to draft an interview guide for these in-depth interviews. Also, during these in-depth interviews, specific cases of diseases (chronic, acute, mild, severe etc.) and medicinal products (cheap, expensive, oral, injection etc.) will be discussed to see if desires, expectations, concerns, and requirements differ per disease area, medicinal product or other variables. Data will be gathered until data saturation. After data saturation has been reached, at least one member of each stakeholder group will be consulted again to evaluate if no important topics were missed. After this meeting either additional interviews will be planned or the interview phase is officially ended.

A report from these interview studies will be used for review in Task 4.2.

Task 2.1 will result in a report on the desires, expectations, concerns, and requirements of stakeholders about methodologies for patient-preferences elicitation (Deliverable 2.1). There will be an interim version of this report to enable WP 3 and WP 4 to advance their objectives earlier.

Task 2.2 Determine the processes, conditions and contextual factors that influence the utility and role of patient-preference studies (Co-lead: KUL + EUR + JANSSEN + CSL; Participants: UU, UMCU, KCE, Amgen, AstraZeneca, Bayer, MSD, Lilly, UNEW, Novartis, Roche, Takeda, EMC, with the Stakeholder Advisory Groups). (M1-13)

The aim of this task is to identify the existing processes, conditions, and contextual factors that have broad and meaningful influence on patient-preference assessment and application and when they are most beneficial (or when they may not be beneficial). The activities are organized in a 3 step approach: a literature review, focus-group discussions,
and in-depth, semi-structured interviews with similar methodologies as used in Task 2.1. Existing initiatives such as MDIC’s patient-centered benefit-risk framework, IMI PROTECT, IMI ADAPT SMART (Accelerated Development of Appropriate Patient Therapies—a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes), IMI EUPATI, and work by the FDA will serve as critical background for this task.

While tasks 2.1 and 2.2 are described separately due to the distinct nature of the data being gathered in each task, the stakeholders whose opinions will be gathered for each task are nearly identical. For this reason, to lessen the burden on stakeholders, to reduce resource requirements and to simplify project logistics, the focus groups and interviews will cover both tasks simultaneously as much as possible.

**The Task covers 3 steps:**

1. **Literature study:** The result of the literature study will form the basis for the focus group discussions (FGD) and semi-structured interviews.

**Strategy:**
In order to perform the literature study, we will start with a background reading exercise, consulting textbooks, articles and reports to get a grasp of the context of the topics and the terminology used in discussions. We will supplement this with a consultation of the six stakeholder groups (i.e. patients, physicians, academics, industry, regulators, and HTAs) to gather their first insights into existing processes, conditions and contextual factors that have broad and meaningful influence on patient-preference assessment (see also task 2.1; due to practical reasons we will contact these stakeholder groups just once by integrating task 2.1 and 2.2). We will identify at the outset as much as possible of the key terminology associated with the topic. This will include important authors, theories / concepts, key research reports or legislation, major movements. Existing initiatives such as MDIC’s patient-centered benefit-risk framework, the Clinical Trials Transformation Initiative (CTTI), IMI PROTECT, IMI ADAPT SMART (Accelerated Development of Appropriate Patient Therapies—a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes), IMI EUPATI, and work by FDA CDER and FDA CDRH as well as by patient advocacy groups National Health Council, FasterCures, Parent Project Muscular Dystrophy, Juvenile Diabetes Research Foundation may serve as critical background for this task.

The identification of key terminologies and their alternatives are important to define the search keywords. Further, we will identify the data bases for search, which are general scientific databases (like PubMed, Embase, PsycINFO) and topic-specific databases as well as websites (for instance of regulatory bodies), patient group reports/whitepapers and other grey sources of information. Based on this input, we will design the literature review. The literature review method itself includes defining the inclusion and exclusion criteria to identify potentially relevant articles, search strategies to retrieve articles or other documents, and a system of scoring published studies for completeness and relevance.

The search will cover 1) existing processes and 2) conditions and contextual factors. For the existing processes, it may include processes at early levels of drug development as well as at market authorization and market access level. We will also consider differences between drug, biologic and medical device development. The conditions and contextual factors may include stages of the medicinal product life cycle, patient cohort involved (age, disease severity, stage of disease, patient motivation, etc.), current information on benefits and risks, the nature of the benefits and harms, time available, medical need, budget, audience for the analysis, research questions being addressed, prior use of the preference-assessment methods in this context, ability of patients to participate in the case studies, cognitive burden for participation, ability to clearly communicate results and ability for the results to inform sponsor, Regulatory Authority, HTA body, reimbursement agency, and patient group decisions.

A report from this literature study in Task 2.2 will be used for review in Task 4.1 and 4.2.

2. **To perform focus-group discussions (FGD) with stakeholders in the Patient Advisory Group, Regulatory Advisory Group, and the HTA Advisory group, as well as with physicians, industry, and academic experts residing in different European countries reflecting different systems for health care and decision making. These discussions will form the basis for in-depth, semi-structured interviews with representatives of all stakeholders.**

Each of the focus groups will be divided into 2 sections focusing on 2 different areas (see also task 2.1; due to practical reasons each focus group will receive questions related to tasks 2.1 and 2.2): 

a. **The (existing) processes wherein patient preferences are implemented/included, such as in some regulatory agencies or industry processes.**

b. **The conditions and contextual factors that are important while dealing with patient preferences, as highlighted in**
For further methodological details this step, see task 2.1, step 2. The topics covered in tasks 2.1 and 2.2 may be addressed in the same focus group meetings, depending on the complexity of the focus group guides and time available. A report from the focus group discussions will be used for review in Task 4.2.

3. To conduct in-depth, semi-structured interviews with all the stakeholders until saturation has been reached.

Strategy
At the start of the interview research, the team will gather and an instruction session for all team members on interview approach will be organized. Written consent will be obtained from all participants, interviews will be recorded and transcribed verbatim using a transcription protocol.

We will use a purposive sampling approach, whereby stakeholders (patients, regulators HTA advisors, physicians, industry, and academic experts) from different European countries will be selected. The protocols may be translated into different languages.

Based on the list of stakeholders that was collected in the previous step, people who did not receive an invitation to the focus groups discussions or who declined focus group participation will be invited for an in-depth interview. This will, again, be based on country of residence (see also task 2.1; due to practical reasons we will integrate this task 2.2 with the in-depth interviews of task 2.1). The number of focus group discussions will be identified during the planning phase for this task.

The outcomes of the literature review and focus groups discussions will be used to draft the interview guide for the in-depth interviews which will address the topics mentioned as most important and the topics that need clarification. Data will be gathered until data saturation (see task 2.1, step 2). After data saturation has been reached, at least 1 member of each stakeholder group will be consulted again to evaluate if no important topics were missed. After this meeting either additional interviews will be planned or the interview phase is officially ended.

A report from these final interviews will be used for review in Task 4.1 and 4.2.

This task will generate a report describing existing processes, conditions, and contextual factors that influence the utility and role of patient-preference studies and the rationale behind such influence (Deliverable 2.2). There will be an interim version of this report to enable WP 3 and WP 4 to advance their objectives earlier.

Task 2.3 Identification of assessment criteria used at decision points throughout the medicinal product life cycle (Lead: UU; Participants: JANSSEN, EUR, UMCU, KUL, KCE, IEO, PAG, Lilly, MSD, Roche, Abbvie, with the Stakeholder Advisory Groups) (M4-13)

The aim of this task is, in parallel with Tasks 2.1 and 2.2, to identify the decision points and the assessment criteria used in the medicinal product life cycle, as well as how the decision points and criteria differ for different stakeholders. If necessary, additional literature review and interviews with the Patient Advisory Group, the Regulatory Advisory Group, the HTA Advisory Group, physicians, industry members, and academic experts will be conducted.

This task will generate a report characterising the decision points throughout the medicinal product life cycle, the activities that are carried out in each step, and the types of assessments made at these points, as well as the assessment criteria used by different stakeholders at each (Deliverable 2.3). There will be an interim version of this report to enable WP 3 and WP 4 to advance their objectives earlier.

Task 2.4 Identification of preference elicitation methods (Co-lead: EUR + SARD; Participants: UU, UMCU, KUL, JANSSEN, Actelion, Amgen, Bayer, IEO, AstraZeneca, Lilly, MSD, UNEW, Roche, Takeda, EMC) (M1-6)

The aim of this task is to conduct a systematic review using peer-reviewed articles across Medline, Econlit, Embase, and PsychInfo. This review will require developing a set of criteria for determining which methods, both qualitative and quantitative, to include and exclude. Additionally, existing summaries (e.g. MDIC’s patient-centered benefit-risk framework) will be reviewed and key experts in the field of preference elicitation will be interviewed as needed.

This task will generate a report describing existing qualitative and quantitative methods for measuring patient benefit-risk preferences in medical treatment (Deliverable 2.4).
### Task 2.5 Identification of educational and psychological feature methods

(Lead: UU; Participants: EUR, KUL, UMCU, IEO, MB, Actelion, MSD, UNEW, Roche, Takeda) (M1-13)

The aim of this task is to identify educational and psychological feature methods, such as serious games (scenario-based educational tools) that can be incorporated in preference elicitation methods. Potential roles for these methods include:

- defining psychological profiles that can be used to ensure representativeness of preference study sample populations
- defining psychological profiles that can be correlated with preference study results
- assisting in preparing patients to understand and perform benefit-risk trade-off tasks
- serving as a platform in which the actual tradeoff tasks are integrated

The task has four steps:

1. to perform a literature study on risk communication, shared decision making and decision aids.
2. to develop a list of psychological and educational tools, including serious games, that can be used as integrated elements in methods of preference elicitation. Patient preferences are likely influenced by demographic factors (age, gender, socio-economic or cultural background). Psychological methods can identify cognitive biases, heuristics, and attitudes and their clusters that drive patient decision making. Educational tools/games have the potential to engage patients personally and encourage patients them to reflect on the subjective impact of specific benefit-risk tradeoffs.
3. to develop a conceptual description of how and why these tools can be useful when integrated into qualitative and quantitative methods for measuring patient preferences in medicinal product benefit-risk assessment.
4. to assess feasibility, time, target patient groups or subpopulations, and necessary conditions and potential methodological issues with regard to educational tools

This task will generate a report on the types and possible role of risk communication, patient's decision aids, psychological instruments and educational tools in measuring patient preferences (Deliverable 2.5).

### Task 2.6 Characterise and appraise the methods

(Lead: EUR + SARD; Participants: UU, KUL, UMCU, IEO, MB, MSD, UNEW, Actelion, Amgen, JANSSEN, Lilly, Roche, Bayer, Takeda, EMC) (M7-18)

This task has three steps:

1. to develop criteria by which to characterize and appraise the methods, including how the patient-preference results are applied to decision making and the relevance of the methods to the factors listed in Tasks 2.2. Existing criteria, such as those in ISPOR guidelines and MDIC’s patient-centered benefit-risk framework will be used to inform these criteria. These criteria should cover issues relevant to the qualitative assessments used in early development, the more quantitative needs for full development, the needs of regulatory review, and HTA- and reimbursement-related assessments. Separate criteria may be needed for qualitative and quantitative methods.

   These criteria may include methodology-related ones such as determination and definition of attributes and levels; sample-related criteria such as maximum/minimum sample size and cognitive demandingness; analysis-related criteria, e.g., of statistical methods; and output-related such as capacity to capture heterogeneity in preferences across patients and across time. Other potential criteria include assessments of internal validity measures, stability to variations in sample size, sample source, attribute list, attribute definition, vignette method, etc. Criteria will also include operational aspects of the case studies such as cost, time, staff, expertise, complexity, and ability to communicate the results to key stakeholder groups and how well industry, Regulatory Authorities, HTA bodies, and reimbursement agencies can collaborate on the design and interpretation of the case studies.

2. to define evaluation scales for these criteria
3. to assess the performance of the methods on these criteria, generating a gap analysis for criteria performance measures that are unknown or uncertain.

This task will generate a report on the criteria to be used to assess the performance of patient-preference methods, the performance of the methods on these criteria, and a gap analysis (Deliverable 2.6).

### Task 2.7 Identification of candidate methodologies and criteria to assess empirical case and simulation studies

(Co-lead: EUR + JANSSEN; Participants: UU, KUL, UMCU, IEO, MB, MSD, Actelion, Amgen, Novartis, Bayer, Roche, SARD, Takeda, EMC, with Stakeholder Advisory Groups (M7-18))
This task has four steps:

- to develop a set of criteria for determining which of the methods assessed in Tasks 2.4 and 2.5 to include and exclude in the case studies. A semi-structured interview or survey of experts on preference elicitation will be conducted.
- using these criteria, to develop a list of available methods (including adaptations to the existing methods) that can potentially be used in the empirical case studies and in the simulation studies. Different lists may be used for the empirical case studies and the computer simulations.
- to assess what metric(s) can be used to assess the “difference” or “distance” between preference study results; i.e., what can be said about whether two studies yield similar or different results.
- to define the criteria to be used to assess the case studies. This task will determine what means will be used to assess the conduct and results of the case studies. Assessments may include:
  - external validity measures, if appropriate and possible
  - internal validity measures, stability to variations in sample size, sample source, attribute list, attribute definition, vignette, method, etc.
  - operational aspects of the case studies such as cost, time, staff, expertise, complexity, and ability to communicate the results to key stakeholder groups

A potential assessment that will be considered is how well industry, Regulatory Authorities, HTA bodies, and reimbursement agencies can collaborate on the design and interpretation of the case studies. Just as industry and Regulatory Authorities collaborate on the design and conduct of clinical trials, they can also potentially collaborate on the design and conduct of patient-preference studies. External Regulatory Authority, HTA body, and reimbursement agency experts can review the case study protocols and provide comments, then can review and comment upon the value of the case study results, thereby providing a small simulation of the value of collaboration among these groups in this area. Assessment of the simulation case studies may include stability of the results to minor perturbations in the simulation, the degree to which the simulation algorithms represent the complexity of real-world preference assessment, the degree to which a simulation can be used to reproduce the results of one or two of the empirical studies, and the degree to which the simulations provide both theoretical and practical insights.

This task will generate a report on the candidate methodologies and assessment criteria to go forward for testing in empirical case studies and simulation studies (Deliverable 2.7).

**Task 2.8 Develop study synopses and preliminary research questions for empirical case studies and simulation**

(For Lead: EUR + Bayer + Actelion; Participants: UU, UMCU, KUL, AstraZeneca, JANSSEN, SARD, EMC, with Stakeholder Advisory Groups) (M7-47)

The aim of this task is to provide requirements and preliminary research questions for WP 3’s empirical case studies and simulation studies. Select members of the Patient Advisory Group, Regulatory Advisory Group, and HTA Advisory Group, and physicians, industry, and academic experts, will be interviewed for this task. While empirical case studies can be used to evaluate how different patient groups may produce different results, the space of the patient preference is limited. In other words, there may not be enough variance in the preference from the empirical studies. Simulation studies, on the other hand, offer a much broader range or space of preference. In fact, thousands and millions of utility values can be generated from simulation studies, which will enable us to build different parameters for different models. Simulation studies can be used to achieve objectives as follow: (i) to understand the impact of variables we can control (such as different attributes) as a function of utility space, (ii) to evaluate which methods will give similar or different results, (iii) to produce results that can be used as a starting point for the empirical studies, and (iv) to use the results from the empirical studies to parameterise the simulations (use the empirical study results as a starting point).

This task has two steps:

- to develop study synopses including preliminary research questions as well as key elements of the empirical case studies and simulations to enable them to address the questions in Task 2.1 and the assessment criteria in Task 2.7 (the studies that will be fleshed out in detail and conducted in WP 3). Possible study designs include using multiple methods to assess preference in the same population, using the same method on separate populations, and using variants on the vignettes, attribute list, attribute definition, pretesting, survey training, regression approach, and other components of preference studies.
- to outline the types of questions that the simulation studies are expected to address, including the design of the “space” of simulated patient utilities and the properties/parameters of preference-assessment methods whose impact will be studied in detail. Example questions include: How do the methods perform when the attributes
have very disparate utilities versus very similar utilities?  How do the methods perform when there is considerable uncertainty on utility or considerable population heterogeneity in utility?  How similar are the results from different methods as a function of properties of the simulated patient utilities and as a function of changing parameters in the methods?

This task will generate study synopses for the case studies and a report on the parameters for empirical case studies and simulation studies (Deliverable 2.8).

This task will be conducted iteratively with WP 3 and continue throughout much of the WP 3 timeline. As empirical case studies and simulation studies are conducted, insights from these studies will be used to update the draft report from this task.

**Task 2.9 Give expert notes about patient-preference methods in view of different disease areas and stages**

(Co-Lead: EUR + UU + JANSSEN + SARD, Participants: EMC) (M18-48)

The aim of this task is to provide notes about patient-preference methods in view of different disease areas and stages, for consideration by WP 4. There are no formal deliverables for this task.

<table>
<thead>
<tr>
<th>Deliverables (brief description and project month of delivery)</th>
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<tbody>
<tr>
<td>D2.1 - Report characterising the desires, expectations, concerns, and requirements of stakeholders about methodologies for patient-preference elicitation (KUL + UU + Takeda + CSL, R, PU, M13)</td>
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<tr>
<td>D2.2 - Report describing existing processes, conditions, and contextual factors that influence the utility and role of patient-preference studies and the rationale behind such influence (KUL + EUR + JANSSEN + CSL, R, PU, M13)</td>
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<tr>
<td>D2.3 - Report characterising the decision points throughout the medicinal product life cycle, the activities that are carried out in each step, and the types of assessments made at these points, as well as the assessment criteria used by different stakeholders at each (UU, R, PU, M13)</td>
</tr>
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<td>D2.4 - Report describing existing qualitative and quantitative methods for measuring patient benefit-risk preferences in medical treatment (EUR + SARD, R, PU, M6)</td>
</tr>
<tr>
<td>D2.5 - Report characterising the types and possible role of psychological instruments and educational tools in measuring patient preferences (UU, R, PU, M13)</td>
</tr>
<tr>
<td>D2.6 - Report characterising the criteria to be used to assess the performance of patient-preference methods, the performance of the methods on these criteria, and a gap analysis (EUR + SARD, R, PU, M18)</td>
</tr>
<tr>
<td>D2.7 - Report describing the candidate methodologies and assessment criteria to go forward for testing in empirical case studies and simulation studies (EUR + JANSSEN, R, PU, M18).</td>
</tr>
<tr>
<td>D2.8 – Report describing the requirements for patient-preference elicitation case studies to inform benefit-risk decision making for industry, Regulatory Authorities, HTA bodies, and reimbursement agencies at different decision points in the medicinal product life cycle (EUR + Bayer + Actelion, R, PU, M47)</td>
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Work Package 3: Case studies

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Objectives

The general objective of WP 3 is to design, execute, and evaluate case studies as defined in WP 2 and to provide WP 4 with results and conclusions ready for translation into recommendations.

The specific objectives of WP 3 are to:
- translate the preliminary research questions and study synopses as defined within WP 2 to concrete study designs and protocols for the academic-led and industry-led case studies
- to support the operational aspects of conducting all case studies
- to support the conduct of case studies with appropriate scientific rigor
- to evaluate the outcomes of the case studies versus a priori criteria defined in WP 2 and to perform cross-case study assessments
- to provide WP 4 with results and conclusions ready for translation into recommendations

Description of work: Overall approach

The coordinating partners of WP 3 are UMCU and Actelion. Both partners will oversee all the tasks described in this document, including the methodological and operational aspects of conducting the case studies in this WP. They will support the learning process between case studies, and will be responsible for drafting final reports where they are the lead partners. For the tasks where other lead partners have been identified, the coordinating partners will provide support for the design and conduct of the case studies and for drafting of the final reports. The coordinating partners of WP 3 will facilitate the communication with other WPs which includes the dissemination of case study results to those WPs. Four academic lead partner(s) were identified during the development of the full proposal and are UB, UKER, UNEW, and ITB; additional industry and/or academic lead partners will be identified during the course of the project. Each lead partner (academic or industry) will undertake the responsibility for conducting specific case studies in their respective disease areas of interest. They will be responsible for drafting the work plan, writing protocols, supporting patient recruitment, collecting and analysing the data, and drafting the final reports. The coordinating partners will support the respective lead partners in all these tasks.

Industry partners who have conducted and reported preference studies prior to the launch of the project will be asked to provide the aggregated results of these study(ies) or provide patient-level data for further analysis. These studies will be classified as ‘historical case studies’ and will be assessed and included in the WP 3 case studies within Task 3.3. Industry partners across the entire consortium will also be requested during the progression of WP 3 to lead a prospective case study(ies); the attending tasks related to this involvement of the industry partners are further defined in Task 3.4.

There are several other partners participating in WP3: UKER, UU, EUR, IEO, MB, European Federation of
Historical case studies by the industry partners will be purely voluntary and this task will be managed by the WP and research questions; pertinent to the PREFER objectives. Industry partners who have previously conducted preference studies among patients may hold valuable data that contribute their knowledge and expertise to the design of the case studies including the translation of the research questions into case study designs. Findings from the mapping of WP will be utilised for conducting preference research. IEO will be included in the case studies where it is decided to include an educational tool (e.g., a serious game), cognitive profiling, or psychological analysis. MB will be included in the case studies where it is decided to include a serious game.

Task 3.1. Drafting of research templates for the case studies (M7-15) (Lead: UU; Contributing: UMCU, EUR, UB, UKER, UNEW, ITB, IEO, Actelion, Merck, Pfizer, AbbVie, EMC)
This task will begin with the collection and assessment of research templates currently in use by academic and industry partners. It further involves the adaptation of the existing templates to the needs of the WP 3 tasks and will follow guidelines for best practice as identified by WP 2 (Task 2.6). A number of important tasks for the case studies will be guided by the research templates, including initial study synopses, study protocols, informed consent forms, statistical analysis plans (SAP), data management specifications, and case study reports. Each template will provide recommendations for describing the design, conduct, data management, and reporting that will be required for each of the case study tasks (Tasks 3.5-3.8). This task will result in several draft (M11) and final research templates (M15) to be used for each of the case study tasks, guaranteeing that the design, execution, and reporting of all case studies will be consistent and of high quality.

Task 3.2. Translate the preliminary research questions identified in WP 2 to concrete study designs (M12-33) (Lead: UMCU; Contributing: UU, EUR, KUL, UKER, UB, UNEW, ITB, IEO, Actelion, Pfizer, Bayer, SARD, CSL, Lilly, KCE, MDUK, IAPo, ECPC, EMC, with the Stakeholder Advisory Groups)
This task involves joint work with WP 2 (Task 2.8) in the mapping of the research questions to the preliminary design and planning of new case studies. Based on the needs of various stakeholders (patients, Regulatory Authorities, industry, HTA bodies, and reimbursement agencies) identified in WP 2 (Tasks 2.1 and 2.2), a set of preliminary research questions will be formulated to be addressed by the case studies. The preference elicitation methods identified in WP 2 will then be mapped to the research questions and decisions will be made as to how many case studies will be initiated. At present, three disease areas have been identified for the conduct of new case studies, i.e., RA, NMD, and lung cancer. The three disease areas span the PREFER criteria matrix for the inclusion of case studies (e.g., involve patients in different age groups, with diseases that are more or less serious, treated by drugs that are relatively cheap or expensive). It has been agreed that current academic relationships and patient alliances within the three disease areas will be utilised for conducting the first wave of case studies while new disease areas may be added according to the identified research questions and methodologies. These additional case studies may be led by academic partners or industry partners. As outlined in Tasks 3.3 and 3.4, industry-led case studies may take the form of either historic or prospective case studies. The mapping of the preliminary research questions identified in WP 2 to industry-led studies will be done on a case-by-case basis to ensure relevance to the PREFER objectives. Patient organisations will contribute their knowledge and expertise to the design of the case studies including the translation of the research questions, drafting the study protocols, supporting patient recruitment, and identifying specific subgroups of the patient population at the earliest point in this task. In addition, the three stakeholder advisory boards will be consulted in the task of translating research questions into case study designs. Findings from the mapping of WP 2 results (Task 2.8) to the design and planning of the case studies will be described in a report (Deliverable 3.2) which will be the precursor for the case study protocols.

Task 3.3. Identifying and assessing historical case studies from industry partners (M12–M24) (Lead: Pfizer; Contributing: UMCU, UU, EUR, KUL, Roche, Bayer, JANSSEN, Lilly, Merck, SARD, EMC)
Industry partners who have previously conducted preference studies among patients may hold valuable data that are pertinent to the PREFER objectives. Historical case studies of industry partners will therefore be identified and assessed for inclusion as a PREFER case study (Deliverable 3.3) and may be used to (i) answer (fully or partly) one or more research questions; (ii) provide lessons learned for conducting patient-preference studies within a specific disease area; and (iii) serve as example study(ies) for the translation of case study results to other disease areas. The contribution of historical case studies by the industry partners will be purely voluntary and this task will be managed by the WP 3 lead and contributing partners. Task 3.3 will require (i) communication with the scientific contact(s) in each participating company to broadly identify the preference studies previously conducted by the companies; (ii) work with the WP 2 to map the submitted historical case studies to the preliminary research questions identified; (iii) work with the Steering...
Committee to review the proposed historical case studies to assess whether they contribute to the final portfolio of case studies; (iv) work with the Steering Committee to identify and resolve any intellectual property issues and agree on data sharing; and (v) perform document analysis and/or interviews with scientific employees who conducted the study(ies) to assess the historical case studies as described above. The task will result in a report describing and assessing the historical case studies from industry (Deliverable 3.3).

**Task 3.4. Identifying and supporting prospective case studies from industry partners (M12–M45) (Lead: Actelion; Contributing: UMCU, KUL, UU, EUR, Pfizer, Bayer, Amgen, Astellas, Novartis, ECPC, EMC)**

Industry partners have been requested to consider leading a case study within the PREFER project. The conduct of preference studies as independent studies or as sub-studies within a larger observational or interventional study design will be considered. This task will consist of (i) contacting industry partners to identify who would be willing to conduct a case study; (ii) working with WP 2 to map the intended industry case studies to the preliminary research questions identified; (iii) working with the Steering Committee to review the proposed prospective case studies to assess whether they contribute to the final portfolio of case studies; (iv) working with the Steering Committee to resolve issues around intellectual property rights and commercial sensitivities; and (v) determining the feasibility of industry-led case studies including consideration of industry needs, timelines, and budget. There are several specificities to this task that cannot be fully defined at this point but may include scenarios where (i) an industry partner retains wholly the ownership of the design and conduct of a case study and only shares aggregated results with PREFER; (ii) an industry partner agrees to a joint ownership of the results of a case study with the PREFER consortium and data sharing is determined accordingly; or (iii) an industry partner works in collaboration with third party to design and conduct the case study and joint ownership of the results of the case study is agreed and data sharing is determined accordingly. Issues related to research use versus commercial intelligence may not be relevant to the conduct and analysis of preference studies among patients but will be discussed and decisions taken with the Steering Committee on a case-by-case basis. It is important to the overall project that one or more industry-led case studies are realised. Therefore, a communication strategy will be established to support the scientific contacts within participating companies to proactively address intellectual property concerns, highlight the value of industry-led case studies, and mitigate any potential risks. The task will result in a description of the prospective case studies from industry (Deliverable 3.4). Identified industry case studies will be included and conducted in Task 3.8.

**General description of case study phase (Task 3.5 – 3.8)**

The case study tasks are iterative in nature. They will begin after the first interim report from WP 2 has been delivered, describing the selection of preference method(s) to be tested, the first research questions that have been selected, and the first study synopses that are written. The first three case studies all start within the time window of Month 15 to Month 45. The case studies will begin in a staggered manner to contribute to the iterative nature of the case study phase. Progress reports will be provided by the case study lead every half year for each case study (at Months 21, 27, 33, and 39). Furthermore, final results of each case study will be communicated to WP 2 team who will use this as input for the identification of new and/or improved preference elicitation methods to be tested in subsequent iterations of the case studies. This process of performing case studies and providing feedback to WP 2 (both in the form of progress reports and final study reports) will continue until the end of all case studies in Month 45.

Three disease areas have already been identified as topics for case studies and the academic partners who will lead the case study and the participating patient organisations have also been determined. Although the case study leads and participating patient organisations are primarily based in Western and Southern European countries, it is of utmost importance that preferences as elicited in case studies truly reflect pan-European preferences. For all prospective case studies, existing networks of patient cohorts in Eastern and Southern European countries will be contacted to participate in the prospective case studies. Patient cohorts already known to the consortium and potential candidates for involvement are based in Serbia, Croatia, Slovenia, Czech Republic, Poland, Hungary, Italy, Spain, Portugal (neuromuscular diseases) and Romania, Greece, Hungary, Ukraine and Russia (lung cancer). New case studies to be identified as the project progresses should make a significant added contribution to the project. Proposals for new case studies (academic-led or industry-led) will be monitored via the criteria that are listed in the PREFER matrix for selection of case studies (of which a preliminary version is displayed below). The Steering Committee will be asked to review the proposal of every case study to ensure that this contributes to the final portfolio of case studies that reflects the PREFER matrix of criteria for choice of case studies.

This preliminary matrix describes the criteria for selecting disease areas in which a case study will be performed:
An aim of the project is to include different patient populations. If possible this includes also vulnerable patients which requires an extra attention and responsibility by the PREFER project team and especially the case study leaders as described in the ethics section 5.1 and below.

To follow all IMI ethics requirements properly IMI PREFER will submit:
- a detailed description of each of the study cohorts to IMI before starting the study.
- a copy of the ethical approval by the competent legal local/national ethics bodies prior to commencement of the case study.
- detailed information on consent procedures that will be implemented including the Informed Consent Forms and Information Sheets for each group of patients that will be included in the study (before commencing any research with humans.) Special attention needs to be addressed to persons unable to give informed consent, vulnerable populations and children (as children from which the assent must be obtained).
- details on the procedures and criteria that will be used to identify/recruit research participants before commencing any research with humans.

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<thead>
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<th>Criterion</th>
<th>Lung cancer</th>
<th>RA</th>
<th>NMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population</td>
<td>Patients with advanced disease</td>
<td>At-risk subjects; patients with active RA</td>
<td>Patients with diverse NMD (e.g. Duchenne, Myotonic Dystrophy, Spinal Muscular Atrophy)</td>
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<td>Age range</td>
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</tr>
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<tr>
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<td>Prevention; suppression of symptoms</td>
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**Task 3.5. Conducting case study RA (M15-M45)** (Lead: UB; Contributing: UKER, UMCU, UU, EUR, IEO, Actelion, Pfizer, Roche, EMC, together with the stakeholder Patient Research Partner Group (UB/R2P2))

This task will conduct a preference study among RA patients and will be led by the UB. The UB and the UKER will provide access to patients affiliated with the Birmingham and Erlangen Rheumatology Patient Cohorts, respectively, with support from patient research partners in the Birmingham Rheumatology Research Patient Partnership. In agreement with all partners, the preliminary research questions as defined in WP 2 (Task 2.8) will be addressed using the selected preference-elicitation method(s) for this case study (WP 2, Task 2.8). All relevant information related to the elicitation of preferences in this disease area (published literature, internal reports) from both academic and industry partners (not restricted to the partners of the consortium) will be collected and critically reviewed. A study protocol tailored to this patient population and the specific treatments (either hypothetical or existing and either single-drug, combination of drugs, or combination of drugs and medical devices) will be written. Within the case studies, simulation studies may be added to answer specific sub-questions and function as a sensitivity analysis of the retrieved results. UB and UKER will apply for ethical approval of the case study (and possibly each of the proposed sub-studies) via the appropriate Institutional Ethical Review Board, which should include the informed consent form provided to patients if participating in this case study. The findings will be summarised in a report (Deliverable 3.5) and disseminated as scientific paper(s). It will be assessed whether a comparison of preferences across countries can be performed for this particular case study given the relevance to the research question, availability of international partner universities and patient organisations, time constraints, and budget. A case study may consist of several sub-studies (i.e., variation of the study or analysis using a different methodology, or a study of a specific patient sub-group).

**Task 3.6. Conducting case study NMD (M15-M45)** (Lead: UNEW; Contributing: UMCU, KUL, UU, EUR, IEO, Actelion, Pfizer, MDUK, EMC)

This task will conduct a preference study among NMD patients and will be led by UNEW. UNEW will provide access to patient groups, in cooperation with collaborating patient societies. In agreement with all partners, the preliminary
research questions as defined in WP 2 (Task 2.8) will be addressed using the selected preference-elicitation method(s) for this case study (WP 2, Task 2.8). All relevant information related to the elicitation of preferences in this disease area (published literature, internal reports) from both academic and industry (not restricted to the partners of the consortium) will be collected and critically reviewed. A study protocol tailored to this patient population and the specific treatments (either hypothetical or existing and either single-drug, combination of drugs, or combination of drugs and medical devices) will be written. Within the case studies, simulation studies may be added to answer specific sub-questions and to function as a sensitivity analysis of the retrieved results. UNEW will apply for ethical approval of the case study (and possibly each of the proposed sub-studies) via the appropriate Institutional/Ethical Review Board, which should include the informed consent form provided to patients if participating in this case study. The findings will be summarised in a report (Deliverable 3.6) and disseminated as scientific paper(s).

It will be assessed whether an international comparison of preferences can be performed for this particular case study given the relevance to the research question, availability of international partner universities and patient organisations, time constraints, and budget. A case study may consist of several sub-studies (i.e., variation of the study or analysis using a different methodology, or a study of a specific patient sub-group).

**Task 3.7. Conducting case study lung cancer (M15-M45)** (Lead: ITB; Contributing: UMCU, UU, EUR, IEO, Actelion, Roche, Pfizer, ECPC, EMC)

This task will conduct a preference study among cancer patients led by the ITB. The ITB will provide access to the patient population, in cooperation with collaborating patient societies. In agreement with all partners, the preliminary research questions as defined in WP 2 (Task 2.8) will be addressed using the selected preference-elicitation method(s) for this case study (WP 2, Task 2.8). All relevant information related to the elicitation of preferences in this disease area (published literature, internal reports) from both academic and industry (not restricted to the partners of the consortium) will be collected and critically reviewed. A study protocol tailored to this patient population and the specific treatments (either hypothetical or existing and either single-drug, combination of drugs, or combination of drugs and medical devices) will be written. Within the case studies, simulation studies may be added to answer specific sub-questions and to function as a sensitivity analysis of the retrieved results. ITB will apply for ethical approval of the case study (and possibly each of the proposed sub-studies) via the appropriate Institutional/Ethical Review Board, which should include the informed consent form provided to patients if participating in this case study. The findings will be summarised in a report (Deliverable 3.7) and disseminated as scientific paper(s).

It will be assessed whether an international comparison of preferences can be performed for this particular case study given the relevance to the research question, availability of international partner universities and patient organisations, time constraints, and budget. A case study may consist of several sub-studies (i.e., variation of the study or analysis using a different methodology, or a study of a specific patient sub-group).

**Task 3.8. Conducting additional case studies (M21-M45)** (Lead: UMCU; Contributing: UU, KUL, EUR, IEO, Actelion, Pfizer, Novartis, Lilly, MSD, ECPC, EMC)

Preliminary research questions as identified in WP 2 (Task 2.8) will be mapped to additional patient populations, study methodologies, and treatments. These can be ‘real-life’ case studies evaluating patient preferences for marketed drugs, hypothetical drugs, and/or drugs in development, or they can be simulation studies. A lead partner from the academic or industry (identified prospective case studies from Task 3.4) consortium will be identified. In agreement with all partners, research questions will be addressed using the selected preference-elicitation method for additional case studies. Information related to the collection of preference data in this disease area (published literature, internal reports) from both academic and industry (not restricted to the partners of the consortium) will be collected, critically reviewed, and appraised, and a study protocol tailored to the specific case studies will be written. Within the case studies, simulation studies may be added to answer specific sub-questions and function as a sensitivity analysis of the empirical study results. The Steering Committee will be asked to review the proposals that are written to assess whether they contribute to the final portfolio of case studies that reflects the PREFER matrix of criteria for choice of case studies. The lead partner of each of the case studies will apply for ethical approval of the case study via the appropriate Institutional/Ethical Review Board (IRB) (and possibly each of the proposed sub-studies), which should include the informed consent form provided to patients participating in a case study. In collaboration with all partners, the study will be conducted by the lead partner (to be identified), and the findings will be summarised in a report (Deliverable 3.8) as well as in scientific paper(s). At the time of writing this proposal, the exact number and scope of additional case studies remain undefined.

Further development of this aspect of the proposal will depend on a number of factors including, but not limited to, candidate methodologies and stakeholder questions as identified in WP 2 and not yet covered in Tasks 3.5-3.7, available patient populations, budget and time constraints, and feasibility of integrating case studies within an industry partner’s drug development program.
Task 3.9. Assessment of case studies based on criteria from WP 2 and cross-case study assessment (M28-M48)
(Lead: UMCU; Contributing: UU, EUR, UB, KUL, UNEW, UKER, ITB, Actelion, Pfizer, MSD, Novartis, MDUK, ECPC, EMC, lead partners of additional case studies (either academic or industry), with the Stakeholder Advisory Groups)

This task involves assessing the outcomes of each of the preference case studies based on the criteria defined in WP 2 (Task 2.7). UMCU, UU, EUR and the lead partner of the specific case study will perform an assessment of the case study based on a number of criteria defined in WP 2.

The case study planning, with staggered start of case studies over time and as well staggered assessment of the outcomes of the case studies against the criteria of WP 2, ensures that experiences from earlier case studies can be used in the design and conduct of later case studies.

After completion of all case studies, the results will be compared to gain insight in, among others, performance of methods and generalisability of methods and outcomes. The draft report of this assessment will be discussed with the three stakeholder advisory boards in order to obtain an objective view of whether the case studies, as designed and conducted, addressed the research questions that were identified by stakeholders. This task will run in parallel with the implementation of the case studies and will be performed at the end of each case study with interim reports at Months 34 and 40 and the findings summarised in a final report (Deliverable 3.9).

Task 3.10. Explore if and to what extent the findings of case studies can be translated to disease areas not included in the case studies and applied to various decision contexts (M12-M48) (Lead: UMCU; Contributing: UU, EUR, KUL, UB, UNEW, UKER, ITB, Actelion, Pfizer, AZ, ECPC, EMC, lead partners of additional case studies (either academic or industry), with the Stakeholder Advisory Groups)

This task involves the assessment of the transferability of methods and results of the case studies to other disease areas and the application of these methods to various decision contexts. The lead partner, together with the contributing partners will conduct this assessment for every disease area studied in the respective case studies by combining (i) interviews with stakeholders, (ii) a literature review on translating study outcomes across disease areas and (iii) comparison to historic cases from industry (identified in Task 3.2) and (iv) conduct simulation studies on the abstract “space” of simulated patient utilities to answer specific research questions identified in WP2 (task 2.8) which will support the generalization of methodological issues of preference studies across disease areas and decision contexts. These simulations would begin in M12, while the other components of task 3.10 would start in M28. The three stakeholder advisory groups will be asked to contribute to this task. This task will run in parallel with the case study phase, meaning that this task will be performed at the end of every case study with interim reports at month 34 and 40. Findings will be summarized in a final report (deliverable 3.10).

Deliverables (brief description and project month of delivery)

D3.1 – Preparation of research templates for the case studies (UU, R, CO, M15)
D3.2 – Study protocols showing the mapping of research questions and candidate methodologies identified in WP 2 to concrete study designs (UMCU, R, CO, M15, M21, M27, M33)
D3.3 – Report describing and assessing the historical case studies from industry (Pfizer, R, PU, M24)
D3.4 – Description of prospective case studies from industry (Actelion, R, CO, M45)
D3.5 – Report of case study RA (UB, R, PU, M45)
D3.6 – Report of case study NMD (UNEW, R, PU, M45)
D3.7 – Report of case study lung cancer (ITB, R, PU, M45)
D3.8 – Reports of additional case studies (UMCU, R, PU, M45)
D3.9 – Report assessing the outcomes of the case studies versus criteria from WP 2 (UMCU, R, PU, M48)
D3.10 – Report assessing the extent to which results of case studies can be translated to other disease areas (UMCU, R, PU, M48)
### Work Package 4: Recommendations

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### Objectives

The general objective of WP 4 is to generate recommendations on patient-preference elicitation to inform benefit-risk decision making throughout the medicinal product life cycle, for industry, Regulatory Authorities, HTA bodies, and reimbursement agencies.

The specific objectives of WP 4 are to:

- establish recommendations to support the development of guidance for industry describing **when and how to include patient preferences** to inform benefit-risk decision making throughout the medicinal product life cycle (i.e., in the form of a set of methodologies and procedures suitable for patient involvement), **acceptable to and valuable for Regulatory Authorities, HTA bodies, reimbursement agencies, and industry**.
- define when and how to include patient preferences to support assessment and licensing decision making **by Regulatory Authorities, HTA bodies, and reimbursement agencies**
- develop recommendations on how to communicate with patients and other relevant stakeholders about patient-preference methods in clear layperson language

This WP is crucial for the overall outcome of the project since acceptance both within the industry as well as by Regulatory Authorities, HTA bodies, and reimbursement agencies of the proposed recommendations will depend on the quality and reliability of the results from the case studies obtained in the framework of this project.

### Description of work: Overall approach

The involvement of patient preferences to inform decision making along the whole medicinal product life cycle triggers a diversity of questions by different stakeholders. Depending on the phase (i.e., the decision point in the life cycle) in which such preference information is required or depending on other factors/conditions such as current information on benefits and risks, time available, medical need, budget (see WP 2), several topics are to be identified, among which the type of stakeholder in need of such preference input, the type of patient preference information required, and the type of methodology that fits in a particular situation. In order to generate recommendations suitable for the targeted stakeholders, the WP 4 team will take a solution-focused approach, starting from the needs of the stakeholders.
**Task 4.1 Define the scope of the recommendations** (Lead: KUL, Contributors: KCE, CSL, Novartis, UU, EUR, UMCU, IEO, ECPC, UB, UKER, UNEW, EPF, IAPO, MDUK, Aegina, Astellas, Bayer, Lilly, JANSSEN, Actelion, MSD, Merck, Abbvie, M1-M18)

This task consists of two steps: first a draft scope document will be prepared (Milestone 4.1) with the structure of the final scope document as well as a list of potential topics/themes to be covered. Next, the final scope document will be prepared (Deliverable 4.1) with the final structure and final topics/themes for the recommendations.

For the draft scope document (M1-M9), the WP4 team will select themes to be included in the draft scope document starting from a review of recommendations made by previous projects (PROTECT IMI, MDIC, etc.). In addition, a review of the literature search of Task 2.1 and Task 2.2 (available M3) will be performed to select additional themes to include in the draft scope document (members of Task 4.1 are also present in Tasks 2.1 and 2.2). Consequently, interviews will be performed by the Task 4.1 lead with the 3 stakeholder groups from PREFER (Patients, HTA regulatory and industry, covering the following aspects (as will be described in the interview guide): 1) the format or structure of the final recommendation document (e.g. a matrix and/or descriptive parts) and 2) procedures for acceptability and uptake of new methods in qualification processes at regulatory bodies.

For the final scope document (M9-M18), the final report of Task 2.1 and Task 2.2 (available in M13) will be reviewed to find additional proposed themes.

The WP4 team will prioritize potential themes and propose a final structure of the document to the Steering Committee. The Steering Committee decide on the final selected themes and agree on the final structure of the scope document.

The aim of the project is reaching a common understanding about the methodological issues and recommendations, because the call text states that there is no consensus on how patients’ values should inform the determination of benefit-risk throughout the lifecycle. WP 4 will also clarify how patients’ values and preferences can be balanced against societal values and preferences and formulate recommendations about how to deal with these different sets of values in different stages of the medicinal product lifecycle.

For the recommendations scope document, we will define a practical, appropriate, structured approach. WP 4 will consider diverse types of recommendations. Areas that will be considered when defining the scope of the recommendations are methodologies; how and under what terms the results of patient-preference studies could be incorporated in marketing authorisation and reimbursement applications; and data handling/processing from patient-preference studies (though the scope is not limited to these areas). The work will also include consideration of how to communicate the final recommendations to a lay audience.

To this end, WP 4 will reflect on an easy-to-handle, practical toolbox targeted to the type of stakeholder and development stage. Different formats for recommendations will be considered, like one report with sections defined by the different needs (see WP2, Task 2.1) or a web-based platform.

**Task 4.2 Preparation of operational requirements and best practices for conducting of case studies** (Lead: KUL, Contributors: KCE, CSL, UU, EUR, UMCU, IEO, ECPC, UB, UKER, UNEW, EPF, IAPO, MDUK, Actelion, JANSSEN, EUR, M1-M32)

Starting from the outputs/deliverables from Tasks 2.1 and 2.2, and also considering the defined scope of recommendations (Task 4.1), we will derive generic, high-level operational points to consider for the consistent conduct of the case studies in WP 3 and to support the conduct of patient-preference studies outside of the PREFER project.

For the draft operational requirement document (M1-M11), we will perform a literature review, to review existing best-practice documents, e.g., those published by the Report of the ISPOR Good Research Practices Task Forces, assess those for applicability, and adjust as necessary. The aim is to define the structure for the final operational requirement document, to identify initial operational requirements for the final document and to line up with the Task 2.1 and Task 2.2 to include in their literature search (M1-3), focus group discussions (M2-6) and interviews (M3-9) also operational aspects. We will review the output of the literature search from Tasks 2.1 and 2.2 (M3) to select the operational themes, we review the draft report of Task 2.1 and 2.2 (after the focus group discussions) (M9) to update the operational themes. Finally, we write the draft operational requirement document (M11) to present to WP3 for them to prepare in the case studies.

The Final operational requirement document (M11-M32) will be drafted as follows. We will review the final document from Tasks 2.1 and 2.2 (M13) and update the draft operational requirement document. Further, based on experience and feedback from the WP 3 teams conducting case studies, these operational points to consider will be revised and updated on an ongoing basis. This will allow lessons learned from earlier case studies to be applied by WP 3 teams supporting later case studies.

The WP4 team will prioritize operational requirements, propose prioritized operational requirements to the Steering Committee for further selection of the prioritized operational requirements, whereafter the final document with points to
consider will be prepared (Deliverable 4.2).
This final deliverable is intended as a reference document summarising experience from the PREFER project in a format that can be used outside of the project.

Task 4.3 Creating draft recommendations and testing these for extrapolation to other disease areas and decision points with stakeholder advisory groups (Lead: KUL, Contributors: KCE, CSL, Novartis, UU, EUR, UMCU, IEO, ECPC, UB, UKER, UNEW, EPF, IAPO, MDUK, Astellas, Bayer, JANSSEN, Pfizer, Actelion, MSD, with input from the Stakeholder Advisory Groups, M33 – M51)

Subtask 4.3.1 This subtask will derive draft recommendations (Milestone 4.3) from the Expert Notes prepared by WP 2 (Task 2.9) and WP 3 (Task 3.10) and from the reports generated from WP 2 and WP 3, e.g., reports on methodologies (Deliverable 2.4), the possible role of psychological instruments and education tools (Deliverable 2.5), and assessment of case studies versus agreed criteria (Deliverable 3.9), in alignment with the scope document (Task 4.1).

Subtasks 4.3.2 These draft recommendations will be tested for extrapolation to other disease areas via a presentation to the appropriate stakeholder advisory groups representing other disease areas in order to see how relevant and how usable the results of the case studies (i.e., the methodologies identified and applied in one particular case) are for other disease areas. Focus will be given to an evaluation as to how to find the right balance between uptake by regulators and the project innovative potential. The results from the expert panel discussions will be summarised in a report (Deliverable 4.3).

Subtask 4.3.3 The draft recommendations will also be evaluated according their relevance and usability for decision making at the different decision points along the medicinal product life cycle with the stakeholder advisory groups. The results from the stakeholder advisory group discussions will be summarised in a report (Deliverable 4.3).

Task 4.4 Refinement of draft recommendations and confirming scope (Lead: KUL, Contributors: KCE, CSL, Novartis, UU, EUR, UMCU, IEO, ECPC, UB, UKER, UNEW, EPF, IAPO, MDUK, Amgen, Astellas, Pfizer, Bayer, Lilly, JANSSEN, Actelion, MSD, Merck, AbbVie, M46 - M57)

Subtasks 4.4.1 Based on the outcome of the stakeholder advisory group discussions (Tasks 4.3.2 and 4.3.3), the draft recommendations will be refined.

Subtask 4.4.2 These refined draft recommendations will undergo consultation rounds with stakeholder networks, including with national regulatory authorities, HTA bodies, or reimbursement agencies, as well as other interested parties from the academic and industry world. The aim of the consultation rounds is to make the final recommendations inclusive of multiple stakeholder viewpoints. In case of divergent views, the factors driving this divergence will be assessed and made explicit. The results from the consultation rounds will be summarised in a report (Deliverable 4.4).

Task 4.5 Formulating final recommendations (Lead: KUL, Contributors: KCE, CSL, Novartis, UU, EUR, UMCU, IEO, ECPC, UB, UKER, UNEW, EPF, MDUK, Amgen, Astellas, Bayer, Lilly, JANSSEN, Actelion, Pfizer, MSD, Merck, AbbVie, M56-60)

Starting from the draft recommendations (Task 4.4.1) and the report from the consultation rounds (Task 4.4.2), final recommendations will be formulated aiming at the right balance between uptake by regulators and the project innovative potential. (Deliverable 4.5).
Get feedback from PREFER Advisory Groups

Revised draft taking feedback from 4.3 into account

Get feedback from broader stakeholder network

Final recommendations taking feedback from 4.4 into account

**Deliverables** (brief description and project month of delivery)

D4.1 – Final scope document for recommendations (KUL, R, PU, M18)

D4.2 – Final report on operational requirements for the conduct of case studies (KUL, R, PU, M32)

D4.3 – Report on extrapolation to other disease areas and to other decision phases in the medicinal product life cycle based on feedback from stakeholder advisory group discussions (KUL, R, PU, M51)

D4.4 – Report with draft recommendations after the consultation with stakeholders (KUL, R, CO, M57)

D4.5 – Final recommendations (KUL, R, PU, M60)
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Table 3.1b: List of Work Packages

9 Work Package number WP 1 - WPn
10 Number of participants leading the work in this WP
11 The total number of person-months allocated to each WP
12 Measured in months from the project start date (Month 1)
13 Measured in months from the project start date (Month 1)
Table 3.1c: List of deliverables

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WP 2 – Patient preference elicitation issues and approaches

| 2.1      | Report characterising the desires, expectations concerns, and requirements of stakeholders about methodologies for patient-preference elicitation | 2      | KUL                            | R    | PU                  | 13           |
| 2.2      | Report describing existing processes, conditions, and contextual factors that influence the utility and role of patient-preference studies and the rationale behind such influence | 2      | KUL                            | R    | PU                  | 13           |
| 2.3      | Report characterising the decision points throughout the medicinal product life cycle, the activities that are carried out in each step, and the types of assessments made at these points, as well as the assessment criteria used by different stakeholders at each | 2      | UU                             | R    | PU                  | 13           |
| 2.4      | Report describing existing qualitative and quantitative methods for measuring patient benefit-risk preferences in medical treatment | 2      | EUR                            | R    | PU                  | 6            |
| 2.5      | Report characterising the types and possible role of psychological instruments and educational tools in measuring patient preferences | 2      | UU                             | R    | PU                  | 13           |
| 2.6      | Report characterising the criteria to be used to assess the performance of patient-preference methods, the performance of the methods on these criteria, and a gap analysis | 2      | EUR                            | R    | PU                  | 18           |

14 Deliverable numbers in order of delivery dates
15 According to the following codes:
R = Document, report (excluding the periodic and final reports); DEC = Websites, patents filing, press & media actions, videos, etc.
16 According to the following codes:
PU = Public, fully open, e.g. web; CO = Confidential, restricted under conditions set out in Model Grant Agreement
17 Measured in months from the project start date (Month 1)
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<td>3</td>
<td>Pfizer</td>
<td>R</td>
<td>PU</td>
<td>24</td>
</tr>
<tr>
<td>3.4</td>
<td>Description of prospective case studies from industry</td>
<td>3</td>
<td>Actelion</td>
<td>R</td>
<td>CO</td>
<td>45</td>
</tr>
<tr>
<td>3.5</td>
<td>Report of case study RA</td>
<td>3</td>
<td>UB</td>
<td>R</td>
<td>PU</td>
<td>45</td>
</tr>
<tr>
<td>3.6</td>
<td>Report of case study NMD</td>
<td>3</td>
<td>UNEW</td>
<td>R</td>
<td>PU</td>
<td>45</td>
</tr>
<tr>
<td>3.7</td>
<td>Report of case study lung cancer</td>
<td>3</td>
<td>IT B</td>
<td>R</td>
<td>PU</td>
<td>45</td>
</tr>
<tr>
<td>3.8</td>
<td>Reports of additional case studies</td>
<td>3</td>
<td>UMCU</td>
<td>R</td>
<td>PU</td>
<td>45</td>
</tr>
<tr>
<td>3.9</td>
<td>Reports assessing the outcomes of the case studies versus criteria from WP 2</td>
<td>3</td>
<td>UMCU</td>
<td>R</td>
<td>PU</td>
<td>48</td>
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<tr>
<td>3.10</td>
<td>Report assessing the extent to which results of case studies can be translated to other disease areas</td>
<td>3</td>
<td>UMCU</td>
<td>R</td>
<td>PU</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td><strong>WP 4 – Recommendations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.1</td>
<td>Final scope document for recommendations</td>
<td>4</td>
<td>KUL</td>
<td>R</td>
<td>PU</td>
<td>18</td>
</tr>
<tr>
<td>4.2</td>
<td>Final report on operational requirements for the conduct of case studies</td>
<td>4</td>
<td>KUL</td>
<td>R</td>
<td>PU</td>
<td>32</td>
</tr>
<tr>
<td>4.3</td>
<td>Report on extrapolation to other disease areas and to other decision phases in the medicinal product life cycle based on feedback from stakeholder advisory group discussions</td>
<td>4</td>
<td>KUL</td>
<td>R</td>
<td>PU</td>
<td>51</td>
</tr>
<tr>
<td>4.4</td>
<td>Report with draft recommendations after consultation with stakeholders</td>
<td>4</td>
<td>KUL</td>
<td>R</td>
<td>CO</td>
<td>57</td>
</tr>
<tr>
<td>4.5</td>
<td>Final recommendations</td>
<td>4</td>
<td>KUL</td>
<td>R</td>
<td>PU</td>
<td>60</td>
</tr>
</tbody>
</table>
3.2 Management structure and procedures

The consortium represents a wide range of decision makers and experts in the area of benefit-risk assessments from industry, academia, patient organisations, Regulatory Authorities, HTA bodies, and reimbursement agencies. This will be complemented by scientists and stakeholders who are not part of the consortium but whose perspectives are crucial for the success for this project and subsequent adoption of the project deliverables and processes.

This is reflected in the project architecture, which is made up of a set of components that are described in Figure 5. Individual components are described below bearing in mind that the consortium agreement will have more details on the governance structure.

3.2.1 General Assembly

The General Assembly includes one representative from each partner of the PREFER consortium, with equal voting rights. The General Assembly is the highest decision-making body. The General Assembly will meet at least once annually face-to-face, per teleconference or videoconference and will be responsible for decisions that need to be consulted and/or decided by all participants such as:

- Accession of new participants in the consortium, withdrawal/removal of participants;
- Major changes in the budget allocation;
- Major changes in the work plan

The General Assembly will take decisions preferably by consensus and in any case by majority vote.
The General Assembly will be chaired by the Project Leader (Novartis) or the Deputy Project Leader (Lilly). The Coordinator (UU) or the Deputy Coordinator (KUL) will act as co-chairs. The General Assembly will be assisted by WP 1 Project Management.

3.2.2 Project Leader, Coordinator and their Deputies
The Project Leader (Novartis) is responsible for the overall scientific and project-related management in close collaboration with the Co-Leader (Lilly), the Coordinator (UU), and the Deputy Coordinator (KUL). The Project Leader and Co-Project Leader are responsible for, among other things, coordinating the EFPIA efforts in the project and for reviewing the project deliverables and reports before submission by the Coordinator to the IMI2 JU.

The Project Leader, the Coordinator, and their Deputies closely collaborate on project strategy, on monitoring project activities, and on the adoption of appropriate measures to ensure the project is on track with respect to budget, time, deliverables, and high scientific quality. To ensure project progress and successful deliverables, they closely collaborate with WP 1 Project Management via the Management Board and with all WP leads and their co-leads as well as with the stakeholder coordinators via the Steering Committee.

The Project Leader and the Coordinator approve the periodic reports prior to submission to the IMI JU. The Project Leader and Coordinator jointly agree on withholding any payment if a Beneficiary eligible to receive IMI JU funding is late in submitting or refuses to provide deliverables as agreed.

The Coordinator is responsible for, among other things, coordinating the efforts of the academic partners and acting as a central point of contact between the Beneficiaries and the IMI2 JU and for coordinating and managing the Grant Agreement.

The Project Leader advises the Coordinator on the allocation and distribution of the IMI2 JU financial contribution among Beneficiaries eligible to receive IMI2 JU funding, in accordance with the IMI2 Grant Agreement and the Consortium Agreement.

3.2.3 Management Board
The Management Board provides key management decisions to effectively and successfully run the project.

The responsibilities, amongst others, of the Management Board are:
- ensure overall progress of the project and alignment and common understanding of project tasks, deliverables, milestones, and timelines
- identify project risks and initiate necessary corrective actions
- coordinate and oversee the external and internal communication

Members of the Management Board are:
- Project Leader and Co-Project Leader
- Coordinator and Deputy Coordinator
  With participation of (and no voting rights):
- WP 1 leads and their co-leads including SPM and communication manager
- Patient and HTA stakeholder coordinators (ECPC, KCE), invited as needed based on the agenda

The Management Board has monthly meetings.

The Management Board will be chaired alternately by the Coordinator (UU) and the Project Leader or their deputies according to an agreed and pre-defined agenda.

Operational/management support for the Management Board is provided by the Project Management WP (WP 1).

3.2.4 Steering Committee
The Steering Committee is the:
- forum for the management board to oversee the individual work of each WP together with the WP leads and their co-leads
- forum for the management board, the WP leads, and their co-leads to get advice and consultation from the Stakeholder Advisory Groups (Patients, Regulatory Authorities, HTA bodies) via the stakeholder coordinators.
The responsibilities, amongst others, of the Steering Committee are:

- oversee the individual work of each WP
- gather input from the Stakeholder Advisory Groups and advise on composition of the Stakeholder Network
- gather input from the Scientific and Ethics Advisory Board
- prepare meeting minutes

Members of the Steering Committee are:

- Project Leader and Co-Project Leader
- Coordinator and Deputy Coordinator
- WP 1-4 leads and their co-leads (both public and private) including SPM and communication manager

The Steering Committee has bi-monthly meetings (face-to-face or virtual). The Steering Committee will invite the stakeholder coordinators (ECPC for patients, EMA for Regulatory Authorities, KCE for HT Abodies) to their meetings for advice and consultation as needed. Stakeholder coordinators are entitled to bring agenda items for discussion at Steering Committee meetings (to which the stakeholders affected would then be invited).

The Steering Committee will take decisions preferably by consensus and in any case by majority vote. Voting members are the Project Leader, the Coordinator, and the WP leads. This will include KCE in addition to achieve a setting with equal voting rights between industry and non-industry, with 5 different partners on each side each partner having one vote.

The Steering Committee will be chaired alternately by the Coordinator (UU) and the Project Leader or their deputies according to an agreed and pre-defined agenda. The agenda will differentiate between items relevant for discussion with the WP leads only and those relevant for discussion with the stakeholder coordinators.

Operational/management support for the Steering Committee is provided by the Project Management WP (WP 1).

3.2.5 Work Package leads

There are four work packages:

- WP 1: Project management
- WP 2: Patient preference elicitation issues and approaches
- WP 3: Case studies
- WP 4: Recommendations

Each of the WPs has a public lead, a public co-lead, an EFPIA lead, and an EFPIA co-lead. WP 1 has in addition a professional project management lead (SPM) for all operational project management activities and a communication manager as main responsible person for all communication and dissemination activities.

The WP leads are responsible for the overall and timely progress according to the detailed work plan of their WPs. They ensure that all WP members provide their support as committed to the project and ensure interactions between the different WPs. They are responsible for reporting to the Steering Committee on their achievements and progress. They escalate any issues to the Management Board in time to avoid project delays.

3.2.6 Scientific Advisory Board

The Scientific Advisory Board consists of five members with representation of scientists reflecting the variety of scientific methods and approaches used or of relevance to the project (patient-preference elicitation, drug evaluation, regulatory science, health economics). They have extensive experience, scientific and/or industrial prominence, or leadership within their respective fields of expertise. The Scientific Advisory Board will meet in association with the annual meetings or by a separate web conference and will prepare their comments based on project and WP documentation available (including deliverables) four weeks in advance of the meeting. They will advise the Steering Committee on project orientations and/or any relevant specific scientific issues related to methodologies, case studies, and recommendations developed. The comments by the Scientific Advisory Board and the responses by the consortium will be discussed at an open workshop during the annual meeting and documented in a written report to the Management Board available not later than three weeks after the meeting.
The confirmed members of the Scientific Advisory Board are:

<redacted>

3.2.7 Ethics Advisory Board
All IMI research activities will respect the fundamental ethical principles and the requirements outlined in the guide for IMI proposals. In order to realise the potential of integrating academic research, patient participation, and fruitful collaboration with pharmaceutical companies, ethical, legal, and societal issues need to be sorted out and handled in a way that both promotes patient and public trust. A key concern is to handle patient data between different organisations and across national borders in an ethically sound manner. Requirements of informed consent as outlined in national regulations and decisions by ethical review boards are a fundamental and primary concern. The Ethics Advisory Board consists of four members reflecting the need to address ethical and legal issues as well as patient perspectives within the context of science and drug development.

The Ethics Advisory Board will meet in association with the annual meetings or by a separate web conference and will prepare their comments based on project and WP documentation (including ethics documents) available four weeks in advance of the meeting. The Ethics Advisory Board will advise the Steering Committee on the main ethical practices applied in the project and on potential ethical problems both within the project and as seen from a wider societal perspective in a written report to the Management Board not later than three weeks after the annual meeting. The Ethical Advisory Board reports will be submitted to IMI with the periodic reports.

The confirmed members of the Ethics Advisory Board are:

<redacted>

3.2.8 Stakeholder Advisory Groups with Stakeholder Coordinator and Stakeholder Advisory Board
The three main stakeholders in this project are (i) patients, including patient representatives, children, parents, and care givers; (ii) Regulatory Authorities, and (iii) HTA bodies and reimbursement agencies.

With finalisation of the Description of Action document for this project, stakeholder involvement could be confirmed at different levels:

- as partners in the consortium
  - Patient Organisations: ECPC, MDUK, EPF, IAPO
  - HTA: Belgian Health Care Knowledge Centre (KCE)
- as Stakeholder Advisory Board members
  - Patients: EURORDIS (European Organisation for Rare Diseases)
  - Regulatory Authorities: EMA, Swedish Medical Products Agency, FDA CBER
  - HTA: Canadian Agency For Drugs And Technologies In Health (CADTH), National Institute for Health and Disability Insurance (NIHDI), German Federal Joint Committee (G-BA).

Stakeholder Advisory Board Members as mentioned above are included in the project to widen the perspective of the consortium and to have a broader coverage in Europe, to involve stakeholders from US and Canada, and finally to broaden the impact of the project.

The Stakeholder Advisory Board members are independent of the consortium and with extensive experience in the decision-making process of drug approval, HTA, and pricing decisions (Regulatory Authorities, HTA bodies, and reimbursement...
agencies) and share a strong interest in the objective of this project in how best to elicit and use patient preferences for decision making (all stakeholders including patients).

There might be even more stakeholders to be involved during the course of the project depending on the needs as, e.g., when case studies are planned. For that purpose a wider Stakeholders Network is expected to include (but will not be limited to) completed and ongoing IMI project groups (e.g., EUPATI), additional HTA bodies via EUnetHTA, scientists, and others. The Steering Committee will advise on composition of this Stakeholder Network.

To efficiently manage all stakeholder activities, three Stakeholder Advisory Groups have been built, one per main stakeholder: the Patients Advisory Group, the Regulatory Authorities Advisory Group, and the HTA Advisory Group. The stakeholder activities within the advisory groups will be coordinated by one Stakeholder Coordinator:

- Patients: ECPC
- Regulatory authorities: EMA
- HTA: KCE

The communication between EMA and the consortium will be facilitated by the project leader (Novartis) and the coordinator (UU).

An overview of the stakeholder groups and their members in this project is given in Figures 6-8 below:

---

18 EMA is an external collaborator but no official beneficiary of the PREFER project.
### Patient Advisory Group

**Coordinator:** ECPC

#### Consortium Members
- European Cancer Patients Coalition (ECPC)
- Muscular Dystrophy UK (MDUK)
- European Patient Forum (EPF)
- International Alliance of Patients’ organizations (IAPO)

#### Stakeholder Advisory Board Members
- EURORDIS (European Organisation for Rare Diseases)
The European network for Health Technology (EUnetHTA) was established to create an effective and sustainable network for HTA across Europe and supports collaboration between European HTA organisations. EUnetHTA Joint Action 2 has finished its work in 2015 and the formal work of EUnetHTA Joint Action 3 is going to start in 2016 (reference: http://www.eunethta.eu/news/eunethta-joint-action-3-formal-preparatory-work-starting; accessed February 28, 2016).

KCE is both coordinator of the PREFER HTA Advisory Group and lead of the EUnetHTA Joint Action 3 WP, “Quality Management, Scientific Guidance and Tools” and will use its connections with HTA bodies through the EUnetHTA network to enhance the HTA network during the course of the PREFER project. The intention is to include the PREFER recommendations on patient-preference elicitation methodologies in the set of EUnetHTA Scientific guidances and tools, if approved by the members of the EUnetHTA WP.
Given the overall objective of this project “to establish recommendations with the view of supporting the development of guidance for industry, Regulatory Authorities and HTA bodies on how and when in the product life-cycle to consider patient perspectives on benefits and risks of medicinal products to inform the decision-making process by regulatory authorities and HTA bodies,” the consortium wants to engage stakeholders who represent a wide spectrum of entities and countries so that their views are duly considered.

The Stakeholder Advisory Group (comprising Stakeholder partners in the consortium, the Stakeholder Advisory Board members and possibly further participants via the Stakeholder Network) are expected to give specific input to a number of topics which are relevant for the different WPs. They are not responsible for the outputs (e.g., recommendations) nor do they endorse the project outputs as adopted by the consortium General Assembly.

- determine the needs, expectations, and concerns of the various stakeholders (patients, industry, Regulatory Authorities, HTA bodies, and reimbursement agencies) about the use of patient preferences to support well-informed decisions regarding medicinal products and the assessment of these methods (see Tasks 2.1, 2.8)
- determine the conditions and contextual factors that influence the utility and role of patient-preference studies: review and discussion of a proposal (see Task 2.2)
- define the criteria to be used to assess the case studies: review and discussion of a proposal (see Task 2.7)
- translate the research questions preliminarily identified in the methods WP to concrete study designs: review and discussion of draft report (see Task 3.2)
- assess the outcomes of the case studies versus criteria from the methods WP: review and discussion of draft report (see Task 3.9)
- explore if and to what extent the findings of case studies can be translated to other disease areas: review and discussion of draft report (see Task 3.10)
- define recommendations: participation in discussion meetings (see Task 4.3)

Additional input along the project could be required, for instance while identifying current processes where patient input is implemented.

The advice from the Stakeholder Advisory Group will be documented in meeting minutes or reports and consolidated and presented to the Steering Committee by the stakeholder coordinators (in writing or during face-to-face meetings, as appropriate).

The stakeholder coordinator will contact stakeholder partners and stakeholders from the Stakeholder Advisory Board or from the stakeholder network for specific questions and/or for input to proposals or draft reports (see topics above). This could require occasional participation in meetings for which five annual meetings (virtual or face-to-face) and two extra workshops (face-to-face), one in the beginning of the project and one at the end, are planned. Ideally, the meetings are integrated in other meeting activities (e.g., annual project meeting).

When contacted by the stakeholder coordinator for consultation, it is the stakeholders’ decision to which topic they provide input and which meetings they attend.

WP 1 will establish and maintain a Stakeholder Network repository and document all interactions with the consortium to allow efficient and structured communication. Main communication with the stakeholders will be done via the stakeholder coordinators. Operational/management support for the Stakeholder Coordinators and for the Stakeholder Advisory Board meetings is provided by the Project Management WP (WP 1).

3.2.9 Work Packages

To facilitate project management and monitoring, the project has been subdivided in four WPs. The activities of the WPs have been described in detail in Section 3.1.

The responsibilities of the WP Leads have been given in Section 3.2.d.
3.2.10 List of milestones

As the milestones are critical decision points in the project, they will be monitored by the Steering Committee on a regular basis. If any problems have arisen, decisions on corrective measures will be taken. Milestones identified for PREFER are listed in Table 3.2a.

Table 3.2a: List of milestones

<table>
<thead>
<tr>
<th>Milestone no.</th>
<th>Milestone name</th>
<th>Related Work Package(s)</th>
<th>Estimated date&lt;sup&gt;19&lt;/sup&gt;</th>
<th>Means of verification&lt;sup&gt;20&lt;/sup&gt; of attainment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Communication infrastructure established (i.e., an information repository, e.g., ProjectPlace)</td>
<td>WP 1</td>
<td>Month 3</td>
<td>All project partners have access</td>
</tr>
<tr>
<td>1.2</td>
<td>Establishment of separate data repository for the project.</td>
<td>WP 1</td>
<td>Month 12</td>
<td>Relevant project partners have access</td>
</tr>
<tr>
<td>2.1</td>
<td>Interim report on desires, expectations, concerns, and requirements of stakeholders about methodologies for patient-preference elicitation</td>
<td>WP 2</td>
<td>Month 9</td>
<td>Interim report available to the consortium</td>
</tr>
<tr>
<td>2.2</td>
<td>Interim report describing existing processes, conditions, and contextual factors that influence the utility and role of patient-preference studies and the rationale behind such influence</td>
<td>WP 2</td>
<td>Month 9</td>
<td>Interim report available to the consortium</td>
</tr>
<tr>
<td>2.3</td>
<td>Interim report characterising the decision points throughout the medicinal product life cycle, the activities that are carried out in each step, and the types of assessments made at these points, as well as the assessment criteria used by different stakeholders at each milestone</td>
<td>WP 2</td>
<td>Month 9</td>
<td>Interim report available to the consortium</td>
</tr>
<tr>
<td>2.4</td>
<td>Interim report on identification of candidate methodologies and criteria to assess empirical case and simulation studies</td>
<td>WP 2</td>
<td>Month 11</td>
<td>Candidate methodologies identified for use by WP 3</td>
</tr>
<tr>
<td>3.1</td>
<td>Initiation of first case study</td>
<td>WP 3</td>
<td>Month 15</td>
<td>Submission of study protocol to ethics committee</td>
</tr>
<tr>
<td>3.2</td>
<td>Agreement on initial industry prospective case study</td>
<td>WP 3</td>
<td>Month 15</td>
<td>Decision of steering committee</td>
</tr>
<tr>
<td>3.3</td>
<td>Initiation of industry prospective case study</td>
<td>WP 3</td>
<td>Month 21</td>
<td>Submission of study protocol to ethics committee</td>
</tr>
<tr>
<td>4.1</td>
<td>Draft scope document for recommendations</td>
<td>WP 4</td>
<td>Month 6</td>
<td>Preliminary Report</td>
</tr>
<tr>
<td>4.2</td>
<td>Draft report on operational requirements and best practices for conducting of case studies</td>
<td>WP 4</td>
<td>Month 11</td>
<td>Preliminary Report</td>
</tr>
<tr>
<td>4.3</td>
<td>First draft of recommendations based on Expert Notes</td>
<td>WP 4</td>
<td>Month 42</td>
<td>Report</td>
</tr>
</tbody>
</table>

<sup>19</sup> Measured in months from the project start date (Month 1)

<sup>20</sup> How it will be confirmed that the milestone has been attained, e.g., a laboratory prototype that is ‘up and running,’ software released and validated by a user group; field survey complete and data quality validated.
### 3.2.11 Critical risks for implementation

#### Table 3.2b: Critical risks for implementation

<table>
<thead>
<tr>
<th>Description of risk</th>
<th>Work Package(s) involved</th>
<th>Proposed risk mitigation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Despite best efforts, no/limited number of case studies from industry</td>
<td>WP 3</td>
<td>Strong communication efforts to help bring in industry case studies, e.g., promoting internal organisation communication strategies, sharing best practices and materials</td>
</tr>
<tr>
<td>Insufficient input from stakeholders during the project</td>
<td>WP 1-4</td>
<td>Reach out to IMI to discuss options for getting stakeholder input</td>
</tr>
<tr>
<td>Lack of impact of final recommendations</td>
<td>WP 1, WP 4</td>
<td>Sharing experience internally and externally throughout the duration of the project; careful consideration of publication and communication strategy such that this information best reaches the intended audience</td>
</tr>
<tr>
<td>Changing needs from stakeholders over time</td>
<td>WP 1-4</td>
<td>As described in governance structure, involve patient, regulator, and HTA advisory groups with a regular monitoring of adequacy of project activities</td>
</tr>
<tr>
<td>Competing initiatives in the same area</td>
<td>WP 2, WP 3, WP 4</td>
<td>Careful monitoring of what is happening in this field; adapting PREFER project based on external environment if necessary</td>
</tr>
<tr>
<td>Case study results show that selected methodologies do not meet the needs of the stakeholders</td>
<td>WP 2, WP 3, WP 4</td>
<td>Sequential running of case studies; learning and adapting throughout the project</td>
</tr>
<tr>
<td>Delays on critical path tasks (causing knock-on delays), e.g., longer than expected ethical board review period</td>
<td>WP 2, WP 3, WP 4</td>
<td>Careful monitoring of project status by WP 1 and creation of plans to take corrective action as needed T horough and early preparation ahead of ethics board approval</td>
</tr>
<tr>
<td>Case studies do not adequately address questions that are most important to key stakeholders</td>
<td>WP 3, WP 4</td>
<td>As described in governance structure, involve patient, regulator, and HTA advisory groups with a regular monitoring of adequacy of project activities</td>
</tr>
<tr>
<td>Outside perception is that case study results cannot be generalised more broadly</td>
<td>WP 1, WP 4</td>
<td>Careful consideration of communication strategy around this issue (e.g., promoting internal organisation communication strategies, sharing best practices and materials)</td>
</tr>
<tr>
<td>Consortium personnel turnover during the duration of a five-year project (leading to loss of project knowledge)</td>
<td>WP 1-4</td>
<td>Good documentation (e.g., up-to-date project status, role descriptions for key personnel), centrally stored; handover plans to be set up in case of personnel turnover. Ideally issue to be flagged early to the steering committee.</td>
</tr>
<tr>
<td>Case study recruitment slower than planned</td>
<td>WP 3</td>
<td>Realistic planning early involvement of investigators and clinical staff; engagement with patient associations</td>
</tr>
</tbody>
</table>
3.3 Consortium as a whole

The PREFER consortium consists of 16 industry partners and 17 academic and SME members including representation from academia, patient organizations, HTA bodies, reimbursement agencies, and project management.

Industry and academic partners provide together broad knowledge and expertise in:
- qualitative and quantitative patient-preference methods
- regulatory, HTA/pricing, and reimbursement decision-making processes
- understanding clinical development, clinical trials, benefit-risk assessment, medical and health affairs
- patient advocacy, behavioural research, and scientific communication to lay audiences

The PREFER consortium built a strong leadership team with members in senior positions in industry and at universities who are experienced in leading departments or research projects and/or who have been involved in earlier IMI projects. The PREFER consortium is complemented by scientists and stakeholders whose perspectives are crucial for the success of this project and subsequent adoption of the project deliverables and processes (see Section 3.2). The governance structure of the project and the broad existing network of the consortium members allow to involve others during the course of the project in case knowledge or resource gaps are identified.

3.3.1 Other countries
Not applicable

3.3.2 Additional partners
Not applicable
5. Ethics

The purpose of the PREFER project is to evaluate methods by which patient preferences may be acknowledged in association with drug development throughout the whole medicinal product life cycle. The expected outcome is to provide industry, Regulatory Authorities, HTA bodies, and reimbursement agencies with recommendations on when and how to elicit patient preferences. The purpose to give patients as major stakeholders in drug development a voice is in itself of ethical significance. Because patient preferences are expected to guide recommendations and policy making it is essential that methodologies proposed represent sound research and that conclusions are based on scientific evidence. It is also important that the patients have been given an opportunity to express their well-informed and reflected preferences. These central requirements have been acknowledged in the scientific description of the proposal. The ethical issues involved in the project are related to protection of privacy and the handling of personal data, including issues concerned with the sharing and access to data. In order to be able to identify and address ethical issues from a wider societal perspective, an independent Ethics Advisory Board with four members, including one patient representative has been appointed (see Section 3.2).

The participants of PREFER agree on adhering to all relevant international, IMI, and national legislation and guidelines relating to the conduct of clinical case studies as detailed below.

All research activities within PREFER requiring approval on ethical and legal grounds through responsible local or national Ethics Committees and Regulatory Authorities will be conducted only after obtaining approval. All ethics approvals will be submitted to IMI before commencement of any clinical case study. A report by the Ethics Advisory Board will be submitted to IMI within the periodic reports.

The proposed research will comply with the highest ethical standards, including those outlined in the Grant Agreement (Article 34 of the Model Grant Agreement) and the European Code of Conduct for Research integrity. The balance between the research objectives and the means used to achieve them will be given special attention. To ensure this, PREFER is supported by its Ethical Advisory Board. The Ethical Advisory Board will consist of four experts on ethics, law, and drug development representing the key areas of the project, including a patient representative. The Ethical Advisory Board will monitor the progress of the project and ensure a high standard of research by taking part in the annual General Assembly meetings. In addition it will:

- provide expert support to the consortium in all relevant ethical questions
- ensure compliance with legislation and guidelines
- conduct regular project reviews
- issue recommendations to the consortium when appropriate

Researchers on all levels participating in the project will receive appropriate training as needed to enable them to carry out their work in adherence to Good Scientific Practice Guidelines and the legal and regulatory framework described in the following sections.

5.1 Humans

The methodologies for eliciting patient preferences will be tested in patient-preference studies. At this stage it is not yet fully decided which patient populations will be involved in the patient-preference studies, but we foresee the possibility of approaching vulnerable patient populations, children, parents, care givers, and healthy volunteers. Each patient preference study requires approval from the relevant national ethical review boards with adherence to requirements related to informed consent and protection of privacy.

Our foremost principles for the conduct of any research involving human participants within PREFER are:

- respect for the rights, integrity, and privacy of patients
- protection of vulnerable patients
- continuous monitoring of patients’ safety
- generation of meaningful, high-quality data
- timely publication of case study results

All research in PREFER involving human participants will be conducted under the applicable international, IMI, and
national laws and regulations and only after obtaining approval by the applicable local or national Ethics Committees and Regulatory Authorities. In particular, the consortium is committed to:

- the Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (Adopted by the 18th World Medical Association (WMA) General Assembly, Helsinki, Finland, June 1964, and last amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013.)
- the standards of the International Conference on Harmonisation/Good Clinical Practice
- the UNESCO: Universal Declaration on Bioethics and Human Rights (2005)

Case studies have not yet been defined in detail. So at this proposal stage it is unclear which countries will be involved. Research with human participants will be conducted in the applicable countries in accordance with national and international regulations. Preference studies regarding future risks or on how to balance benefits and risks may incur psychological distress for, e.g., vulnerable patient groups. This implies that all studies conducted within the PREFER project will have to take actions in order to be able to support/counsel patients appropriately.

As mentioned above PREFER will seek to include a broad selection of patient populations. This includes also vulnerable patients if possible. It is important for ethical reasons that also perspectives from these patient groups are included, patients that may experience difficulties to get their voice heard and their preferences taken into account. Vulnerable patients populations may be identified in particular in the field of Neuromuscular disorders where many of the diagnosed diseases are rare and the patients are minor. This is also why the PREFER project has included a patient organization within this disease area, i.e. Muscular Dystrophy UK. They, as well as the other patient organisations, will be asked to give extra attention to the situation of vulnerable patients and the terms on which they are included in the clinical case studies. As has been described above, preference studies regarding future risks or on how to balance benefits and risks may incur psychological distress for vulnerable patient groups. This implies that all studies conducted within the PREFER project will take actions in order to be able to support/counsel patients appropriately. This will be one of the requirements assigned to each leader of a clinical case study.

5.2 Protection of personal data

No experiments will commence before the consent of patients and approval of relevant local and national ethics committees and Regulatory Authorities have been obtained. The collection of personal data will be conducted under the applicable international, IMI, and national laws and regulations and requires previous written informed consent by the individual and must include a permission to share data in the consortium, i.e., with public and commercial entities and if applicable outside the EU in countries with lower data protection standards (according to the data management plan, see below and Section 2.2).

PREFER researchers commit to the highest standards of data security and protection in order to preserve the personal rights and interests of study participants. They will adhere to the provisions set out in the:

- Directive 2006/24/EC of 15 March 2006 on the retention of data generated or processed in connection with the provision of publicly available electronic communication services or of public communications networks
- Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data
- Upcoming EU General Data Protection Regulation (foreseen coming into effect in 2018)

Prior to collecting, storing, and processing sensitive health data, the consortium will seek approval of the applicable local and/or national data protection authorities and work within the processes recommended in the e-Health Task Force Report “Redesigning Health in Europe for 2020.”

To secure the confidentiality, accuracy, and security of data and data management, the following measures will be taken:

- all personal data obtained within the clinical case studies will be transmitted to partners within the consortium only after anonymisation or pseudonymisation. Keys to identification numbers will be held confidentially within the
respective clinical units. In situations where re-identification of study participants becomes necessary, for example the collection of additional data, this will only be possible through the clinical unit and in cases where informed consent for such cases has been given.

- personal data are entered to secure websites, according to the data management plan (see Task 2.2)
- data are processed only for the purposes outlined in the patient information and informed consent forms of the respective case studies. Use for other purposes will require explicit patient approval. Also, data are not transferred to any places outside the consortium without patient consent.

Access to experimental data will be granted to partners in non-EU countries for restricted use within the PREFER project. Data handling in non-EU countries will be fully conforming to national laws and regulations and the European Directive 95/46/EC. In cases of contradiction, the tighter regulation shall prevail. The necessary and legally adequate measures will be taken to ensure that the data protection standards of the EU shall be complied with (see below). Transfer and subsequent use of data from partners in US will be restricted in accordance with federal and state laws.

None of the personal data will be used for commercial purposes, but the knowledge derived from the research using the personal data may be brought forward to such use as appropriate, and this process will be regulated by the Grant Agreement and the Consortium Agreement, in accordance with any generally valid legislation and regulations.

The following points to consider will guide the collection, use and sharing of data within the PREFER project:

(i) The entity providing personal data to the project shall verify that:
- the initial collection of these data has been compliant with the requirements of the original purpose
- the collection and the provision of the data to the project meets all legal requirements to which the entity is subject
- further storage and processing of the data after completion of the research project is in compliance with applicable law

(ii) The entity which provides personal data to the project shall document any restriction of use or obligation applicable to these data (e.g., the limited scope of purpose imposed by the consent form)

(iii) The secondary use of data in the PREFER project shall only take place using anonymised data, and anonymisation shall be in accordance with state of the art and legal requirements.

(iv) Information and consent procedures shall be approved by the relevant national or local ethics boards.

(v) Data collectors collecting personal data for a prospective collaborative research project shall inform the study participants about the project in an appropriate manner, including:
- the identity of the data controller
- the voluntariness of the collection of data
- the purposes of the processing
- the nature of the processed data, including its type (identifiable, coded, anonymised)
- the handling of the data
- the existence of the right of access to, and the right to rectify the data concerning them
- if the research project reasonably anticipates the sharing of data across research groups (including academic and commercial entities) and national borders (including information about potentially lower data protection standards outside EU)
- if the project involves collaboration with both academic and commercial partners
- that consent may be withdrawn and how this is done

(vi) The entity which uses personal data in the project shall be responsible to ensure that it has the right under the applicable data protection and other laws to perform the activities contemplated in the project.

(vii) Research project results or outcomes should be made available to study participants in a manner allowing non-specialists to understand the results.

(viii) Data transfer agreements should be used with parties outside EU and where there is no Safe Harbour clause, or with countries accepted by the European Commission in accordance with Article 25, Directive 95/46/EC. Using standard EC
contract clauses, e.g. Commission Decision 2001/497/EC, C(2004)5721. Having regard to a recent decision in the Court of Justice of the European Union (C-362/14, Schrems), where the Commission decision on Safe Harbor for transfer of data to the USA was invalidated, it is suggested that in expectancy of further clarifications (e.g. upcoming agreement between EU and the Unites States) of the implications of this ruling for research, that in all collaborations with partners in the USA, the partners enter into a Data Transfer Agreements ensuring an adequate level of protection in relation to European data protection principles.

(ix) Personal data shall always be collected, stored, and exchanged in a secure manner, through secure channels. Stored data will not include any personal identifiers.

(x) Sharing of data shall follow criteria for the acknowledgement of intellectual contributions and originality through rules of authorship and intellectual property rights.

5.3 Non-EU countries
Access to experimental data sets will be granted to partners in non-EU countries for restricted use within the PREFER project. Data handling in non-EU countries will be fully conforming to national laws and regulations and the European Directive 95/46/EC. In cases of contradiction, the tighter regulation shall prevail. Data transfer from US to European partners will be fully conforming to federal and state laws, as well as individual informed consent.

5.4 Misuse
The research conducted in PREFER does not have the potential for malevolent/criminal/terrorist abuse.

5.5 Other ethics issues
There are no other ethics issues currently identified beyond those discussed above. Any potential issues that arise during the project duration will be presented to the Ethics Advisory Board who will ensure they are addressed by taking the appropriate organisational, legal, and regulatory steps.