RESEARCH PROTOCOL

TRADE-OFFS BETWEEN BENEFITS AND HARMS OF DRUGS: A STATED PREFERENCE STUDY WITH ADULT PATIENTS WITH CANCER IN EUROPE

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List of Abbreviations

Term	Definition
Agency	European Medicine Agency
CEA	Cost-effectiveness analysis
CDRH	Center for Devices and Radiological Health
CI	Confidence interval
CLL	Chronic Lymphocytic Leukaemia
CUA	Cost-utility analysis
DCE	Discrete Choice Experiment
EC	Ethics Committee
FDA	Food and Drug Administration
IRB	Institutional Review Board
LOL	Length of life
MCDA	Multiple Criterion Decision Analyses
MM	Multiple Myeloma
NSCLC	Non-Small Cell Lung Cancer
OMEP	Orthogonal main effect plan
PAGs	Patient Advocacy Groups
PP	Patient preference
PRO	Patient-Reported outcome
QALY	Quality-Adjusted Life Year
QoL	Quality of life
SD	Standard deviation
TTO	Time Trade -Off

TRADE-OFFS BETWEEN BENEFITS AND HARMS OF DRUGS: A STATED PREFERENCE STUDY WITH ADULT PATIENTS WITH CANCER IN EUROPE

1. Study Protocol Overview

This is a cross-sectional study where data is collected using a patient preference (PP) survey aiming to assess the patient and disease characteristics that influence cancer treatment preferences towards key endpoints in European patients with cancer. This study will include two phases: A Qualitative Evidence Generation phase with approximately 30 patients with cancer and a Quantitative Evidence Generation phase with approximately 900 patients with cancer. A pilot/feasibility phase with approximately 20 patients with cancer will be included as part of the Quantitative Evidence Generation phase.

The study will be registered in the EU PAS Register (http://www.encepp.eu/encepp/studiesDatabase.jsp) after acceptance of the final protocol, that will summarize both phases of the study. The study will also be submitted for central institutional review board/ethics committee (IRB/EC) approval where required according to local regulations.

2. Background

Cancers are the second highest cause of noncommunicable disease deaths globally, estimated to kill 9 million people each year.[1] Europe has approximately a quarter share of the global cancer burden, with an estimated 1.9 million deaths from cancer in Europe in 2018.[2] The most common cancers in Europe are female breast, colorectal, lung and prostate cancers. These four cancers represent half of the overall cases of cancer in Europe, but around 21 other major cancers and other rarer types of cancer contribute to the epidemiology of cancer across Europe as well.[2]

The introduction of novel drug therapies for cancer has improved survival outcomes for cancers dramatically. However, due to the high toxicity of many novel drug therapies, improved survival outcomes may come at a cost of severe side effects and/or short- and long-term impacts on patient's quality of life (QoL). Short and long term toxicities are well documented in cancers such as breast cancer, liver cancer, multiple myeloma, advanced non-small cell lung cancer and chronic lymphocytic leukaemia.[3-5] Some short and long term toxicities could be life threatening such as cardiac toxicities, respiratory failure and increased risk of secondary primary malignancies, while others not life threatening can have a substantial impact on QoL; such as fatigue, nausea, neuropathy, osteoporosis and infertility. There is also not enough integration of the patient's voice and their preferences around the benefits and harms of new novel drug

therapies when receiving drug approval. Therefore, the benefits and harms of new novel drug therapies and the patient's voice needs to be further considered. Benefits and harms of novel drug therapies are currently considered in a clinical context during regulatory approval, but information about how patients with cancer assess benefits and harms of treatments while of notable interest to regulators, are also not currently routinely considered.

While some novel drug therapies lead to complete remission, other recently approved drugs may only increase survival by several months.[6, 7] Studies of PP in cancer demonstrate that the majority of patients with cancer favour increased survival outcomes from treatments, however in cases where survival benefit is considered modest, and high levels of toxicity are faced, decision making may become more complex.[8] Studies looking at preferences of healthcare professionals and regulators have also demonstrated that while there is a trade-off between overall survival and toxicity, the majority of stakeholders also attach the most weight to overall survival.[9-11] A recent systematic review of the literature on QoL verses length of life (LoL) preferences of patients with cancer between 1942 and 2018, concluded that age, future expectations and better or poorer health were all key determinants of whether patients would prioritise QoL over LoL. Generally those who were older or in poorer health were more likely to prioritise QoL.[12]

PP, also referred to as health preference research, refers to an individual's evaluation priorities for of dimensions of health outcomes and treatment attributes, which may in part influence health care choices.[13] Rooted in economic theory and cognition, patients are asked to make choices between alternative outcomes/treatments and reflect on potential consequences of these choices. A common use for stated PP work and often considered by Health Technology Assessment (HTA) bodies and for pricing negotiation once a drug has been approved by regulatory bodies has been the elicitation of utilities for the eventual purpose of modelling cost per Quality-Adjusted Life Year (QALY). Common to the distinct QALY evaluation methods are that they examine the effect of an intervention and the decision-making rule to optimize effect per cost. In cost-effectiveness analysis (CEA), the effect is a one-dimensional measure such as blood pressure, whereas in cost-utility analysis (CUA) it is a multidimensional measure in which the quality of the life year saved (i.e., QALY) is taken into consideration. An important feature of these health outcomes is that they only allow for health-related preference-based outcome measures, meaning that only health-related measures of benefits are considered.[14]

At present, stated preference studies are not systematically carried out within the context of drug development. In 2016, the Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH) developed a patient-focused guidance document, with a focus on the inclusion of PP research into decision making. The FDA guidance defines PP as "a statement of the relative desirability or acceptability to patients of specified alternatives or choice among

outcomes or other attributes that differ among alternative health interventions".[15] The guidance makes the distinction between Patient-Reported Outcome (PRO) research and PP research, as "PRO instruments are designed to measure a patient's perceptions of health status before, during, and after therapy, while PP studies are designed to measure what specified type of therapy or attributes of a given therapeutic or diagnostic strategy a patient might prefer".[15]

PP research has traditionally been the domain of health/behavioural economists, epidemiologists and market researchers, with the intended use for HTA drug or medical device approvals, and clinical practice guideline development. A recent draft guidance from the FDA[16] supports the notion that patient experience data can be interpreted as information that captures patients' experiences, perspectives, needs, and priorities related to but not limited to (1) symptoms of their condition and its natural history; (2) impact of the conditions on their functioning and quality of life; (3) their experience with treatments; (4) input on which outcomes are important to them; (5) their preferences for outcomes and treatments; and (6) the relative importance of any issue as defined by patients. Numbers one and two are traditionally captured through PROs; number 4 and 5 through PP research, and number 3 through both. This guidance has explicitly opened the door for the inclusion of PP research in the context of drug development. More explicitly, PP research can provide additional insight on the benefits patients seek and how this information can be used to inform decision-making across the drug development lifecycle.

Recent studies conducted by the Europeans Medicines Agency (the Agency) elicited individual PP on three generic attributes: overall survival, long-term moderate toxicity and severe toxicity using multi-criteria decision analysis (MCDA).[17] This was later followed by a larger online survey based on MCDA and swing weighting methods to elicit stated preferences for similar attributes in patients with multiple myeloma.[10] However, how patient, treatment and disease characteristics are associated with preferences of patients with cancer remains largely unknown; cultural, demographic, clinical and psychological characteristics may influence preferences in certain subsets of patients with cancer. It is therefore important to explore the heterogeneity of preferences for different novel cancer treatments. Different subsets of patients with cancer may have different treatment choices, which could inform policy and clinical practice.

3. Study Goals and Objectives

The objectives of this study are to describe stated preferences regarding benefits and harms of novel cancer treatments of patients with cancer in Europe and to understand the heterogeneity in treatment preferences. To do this, there are three main key objectives outlined in this study:

Primary Objective:

1. To identify and describe PP relating to benefits and harms of cancer drugs in patients with both common and rare cancer types

2. To identify and describe the PP towards key endpoints used traditionally to assess the efficacy and safety of oncology drugs in patients with both common and rare cancer types

Secondary Objective:

1. To determine the extent to which patients' heterogeneous characteristics are associated with stated preferences

Exploratory Objective:

1. An exploratory objective is to compare and contrast preference weights and patient characteristics with stated preferences using different stated preference methods (MCDA/DCE/TTO), within the context of the use of these methodologies for regulatory use.

4. Method

4.1. Procedure

4.1.1. *Qualitative Evidence Generation*

4.1.1.1. *Literature review*

A targeted literature review will be conducted to identify different treatment attributes of current marketed treatments in oncology. We have selected a range of rare and more common cancers in adult patients to allow for a more manageable targeted literature review, including late stage Non-Small Cell Lung Cancer (NSCLC), breast cancer, liver cancer, Multiple Myeloma (MM), and Chronic Lymphocytic Leukaemia (CLL). The targeted literature review will aim at identifying the attributes related to oncology treatments in each identified cancer and to identify the language used by patients and oncologists when treating patients. If applicable, treatments for different cancer stages or treatment lines will be assessed separately. The literature review will also aim to identify key characteristics of the patient population, such as age, disease severity, family background, health awareness and literacy, and prior disease history, as potential covariates to examine preference heterogeneity.

The attributes from the literature review will then be compared to the key endpoints typically used for consideration in the approval of novel cancer therapies by regulatory authorities. A final list of

attributes and attributes-levels will be identified to develop a survey assessing cancer treatment preferences and the potential trade-offs made when considering the approval of oncology drugs. These attributes reflecting key endpoints may include progression-free survival, overall survival, and safety. Typically, the total number of attributes ranges from 2 – 8 (no less than 10), with the average number of attributes used in DCE studies is 5.74 (4 – 6 attributes).[18, 19] The number of attributes will aim to align with current guidelines and recommendations for DCE studies. A conceptual model summarizing the attributes and levels identified in the literature will be summarized in a figure. A conceptual model summarizing the endpoints, their potential attributes, and associated-levels will also be described (see Figure 1).

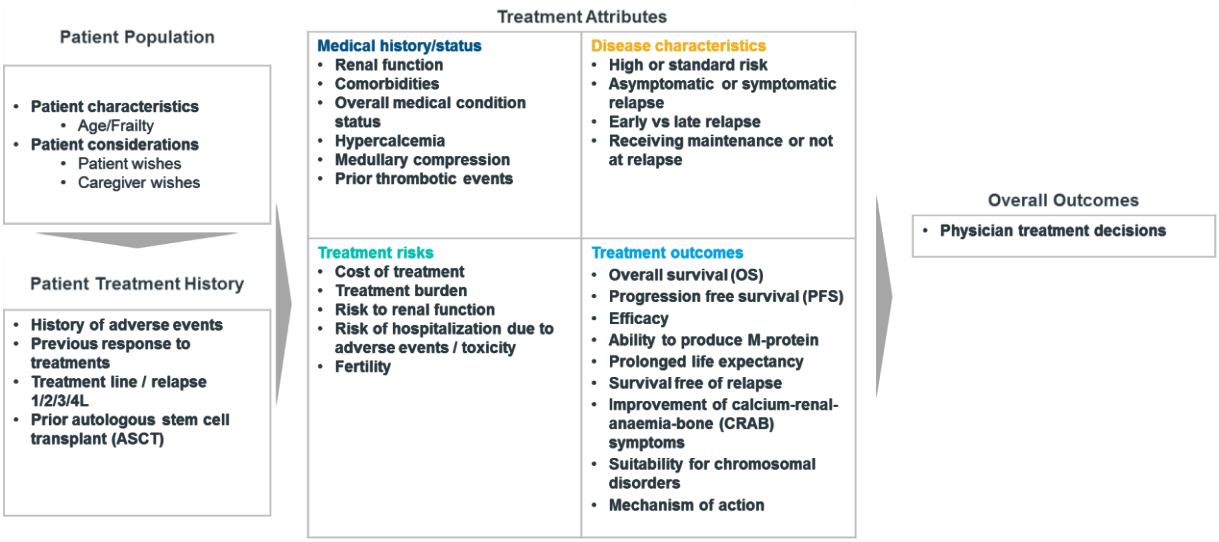


Figure 1. Example of a conceptual model of attributes and levels identified from the literature

4.1.1.2.

Qualitative Interviews

The attributes and identified in the literature review will be used to create clinical vignettes and presented to patients in qualitative interviews. A clinical vignette represents a short case description of the different patient profiles and have been widely used in the clinical research field to assess how clinicians or patients view and make decisions.[21] An example of a clinical vignette and associated attribute levels is presented in Figure 2. Vignettes will be developed to represent

the different hypothetical patient profiles based on a range of common and rare cancer types. The vignettes will contain a written description of a patient's cancer experience and detail treatment-related characteristics and health outcomes/endpoints of interest corresponding to each patient profile. These characteristics will be defined by the endpoints, their potential attributes, and associated levels resulting from the targeted literature review. The vignettes will include different combinations of trade-offs and their levels to describe the endpoints and disease-related characteristics. Vignettes are typically used to help inform the design of a stated preference survey, but it can used to include also to consider the relative importance of attributes influencing choice by checking the validity of these attributes with patients.[21] In previous research, no more than 12-16 vignettes are typically recommended to administer to each participant at a time, as this is considered to be reaching the upper limit of cognitive burden to examine the different hypothetical decisions, but this can depend on the number and type of attributes of interest.[20] Given that a combination of both common and rare cancer types will be aimed to be included, it is recommended to include no more than 6 vignettes to be developed for the qualitative interviews.

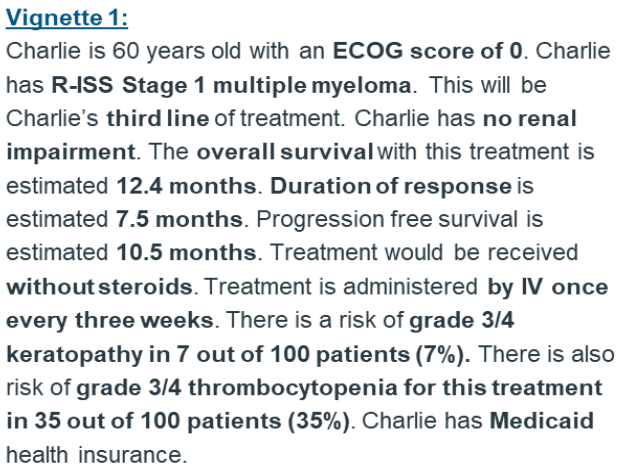


Figure 2. Example of a clinical vignette targeted at physicians (illustrative purposes only)

The Qualitative Evidence generation phase of the study will consist of one-to-one semi-structured concept elicitation (identification of new attributes and levels) and cognitive debriefing interviews (discussing the vignettes and available survey questions) with 30 patients with cancer, such as

patients with late stage NSCLC, breast cancer, liver cancer, MM, or CLL from 2 European countries. The interview guide will be aimed at understanding the factors patients take into account when assessing their preferences and satisfaction with available treatment options provided by their physicians. The interview guide will use a “think aloud” framework designed to encourage patients to verbalize their thought processes and provide input when presented with the vignettes, in accordance with International Society for Pharmacoeconomics and Outcomes Research (ISPOR) recommendations and good practices.[22, 23] The moderators will be trained on the study protocol and interview guide prior to interviewing any patients. Interviews will last approximately 45 minutes and conducted in local language.

Eligible patients will be identified from a screener and if they fit the criteria and are interested to take part, they will receive a link prior to the interview and be asked to join an online conference platform to conduct their interview. At the beginning of the interview, a trained moderator from the IQVIA team will obtain verbal consent, provide the opportunity for patients to ask any questions concerning the study, and will obtain permission to audio-record the interview. During the interview, the moderator will share their screen to present the vignettes one-by-one to patients using the online communication platform. The interview guide will be used to probe on clarity and validity of the vignettes presented. Interviews will be audio-recorded and verbatim will be transcribed and translated into English. Patients will receive an honorarium for the time spent for the interview, which will vary as per fair local market value.

4.1.1.3. *Pilot*

An iterative approach will be used to refine and finalize the vignettes. A first round of interviews, including 15 patients, will be used to identify the wording and framing of the attributes and levels. An equal balance of patients with cancer from two countries (approximately 7-8 patients per country per round) will be included to refine and finalize the vignettes. Refinements will be made to the attributes and associated levels defining the patient profiles and treatment decisions in the vignettes. The revised vignettes will then be debriefed with a second set of interviews with 15 additional patients to further refine the list of attributes and levels. After the attributes and levels are refined, all patients who took part in the qualitative evidence generation phase will be provided the option to be re-contacted to provide feedback on the final list of attributes to be inputted into the survey using a cognitive debriefing approach. Some questions in the cognitive debriefing will also ask patients about their interview experience and burden.

Through the interview phase, general guidelines will be followed to help determine the number of attributes per vignette and the number of combination profiles to be applied to the vignettes.[21] The attribute combinations and anticipated burden in combination with other clinical characteristics will also be prompted with patients during the qualitative phase to identify the

number of attributes that were most important or relevant. This will enable the research team to make decisions during the development of the quantitative survey with respect to the attribute and associated-level combinations to be feasibly included in the survey. The Agency will approve the final list of attributes, associated-levels and vignettes before moving to the quantitative evidence generation phase of the study.

Quantitative Evidence Generation

Development of the survey

4.1.2. The attributes and associated levels most relevant to patients when making a treatment decision, as validated during the qualitative interviews, will be incorporated into a web-based survey. The survey will be programmed online using Qualtrics^{XM} software. Qualtrics^{XM} provides an online survey hosting platform with advanced capabilities for implementing non-standard surveys, including choice tasks and maxdiff experiments.

4.1.2.1.

Pilot/feasibility phase

After the design of the choice sets and draft survey, a pilot/feasibility phase will be conducted with the first 20 patients to assess the comprehension of the choice sets and to identify any issues encountered during completion of the quantitative survey, such as clarity of the questions, understanding of the different choice tasks and what can be improved. This feedback will be reported through open-ended questions at the end of the survey. Based on the input of the pilot/feasibility, necessary refinements will be made to the choice sets and surveys following the feedback from the pilot and before deployment to all patients.

4.1.2.2.

Overview of the proposed quantitative methodologies

Different methods currently exist to elicit preferences; stated preference methods use qualitative, quantitative or mixed-methods approaches to elicit patients' preferences within a hypothetical option context as an experimental framework,[25] while revealed preference methods are based on observed data of patients' actual behaviour therefore implying preference.[26] Stated preferences are more commonly used in the context of drug development as they can provide more insight into the reasons behind patient’s choices. There are around 20 different quantitative methodologies for eliciting stated preferences. Most commonly used are Discrete Choice Experiments, but Time Trade-Off methods, and Multi-Criterion Decision Analysis are also commonly used. All these methodologies across different groups of patients to compare whether the preferences obtained with the different methods lead to similar results.

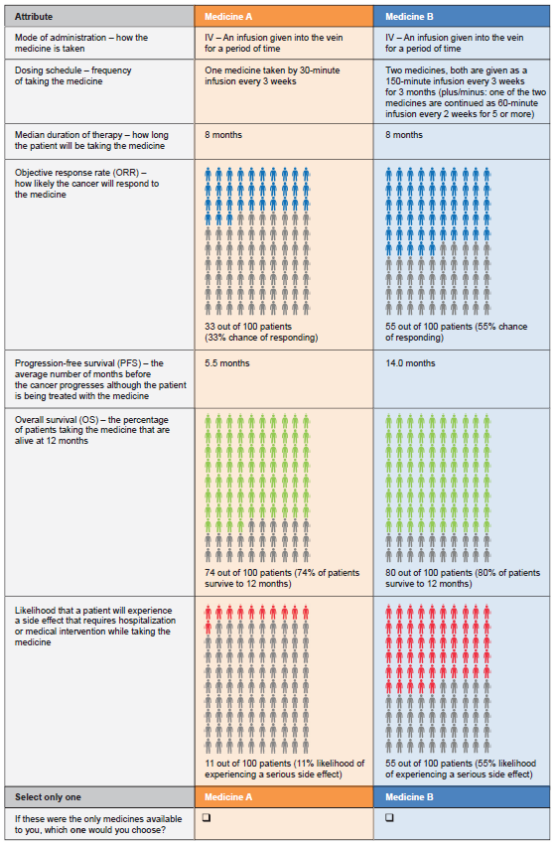
Given the novel application of the use of PP information for regulatory context use, we aimed at eliciting both the PP on the trade-offs between the benefits and risks of oncology drugs, but also trying to understand whether a methodology is superior to another in this novel context. It is known that for cost-effectiveness use, different methods will elicit different utilities, and that there are advantages and limitations of each. We have therefore taken the following approach to compare a subset of these methods. All surveys will include a discrete choice experiment (DCE) task as the leading/primary methodology. In addition, patients will also be randomly assigned to either an additional time trade off (TTO) (n = 450) or multi criterion decision analyses (MCDA) task (n = 450). The order of tasks will be randomly presented to patients i.e. some patients will be presented the DCE first, followed by the TTO or MCDA task, and other patients will be presented the TTO or MCDA task first, followed by the DCE. The web-based survey is expected to take approximately 20 minutes to complete, and the order will also be randomised equally across participants. After completion of the survey, patients will be asked to click on a link at the end to submit their survey for completion. The anonymised data will be automatically saved to the Qualtrics platform.

Discrete Choice Experiment (DCE)

A DCE is a quantitative technique based on random utility theory used to elicit individual preferences for different hypothetical alternatives for treatment. The assumption of a DCE is that choices among sets of alternative profiles are motivated by differences in the levels of the attributes that define the profiles.[24, 27] A DCE allows researchers to quantify the impact of changes in attribute-levels on choice and to understand the strength of preference for changes in attribute-level. The DCE method also allows for hypothetical choices to be incorporated in multiple attributes and levels to be used in simulated realistic scenarios. For example, a patient or patient must weigh both efficacy and side-effects simultaneously.

Respondents evaluate trade-offs when deciding about different treatment options, each consisting of numerous attributes, as it is done in the real-world setting. The design of a DCE usually consists of a choice-based task that enables the simultaneous assessment of multiple attributes and levels to be presented and assessed. During the DCE, patients are presented with a pairwise choice set in the form of two alternative profiles. The choice set will comprise of all attributes and associated attribute-levels finalized from the feasibility phase. The levels of the attributes will vary in each choice set of the DCE. Patients will be asked to choose a preferred choice set out of the 2 alternatives. Patients will be presented with an illustrative example of a pairwise choice set as well as definitions of all attributes and associated attribute-levels, before being asked to state their preferences (see Figure 3 below as an example). The selection of choice sets that each patient will complete are determined via experimental design.

For this study design, an orthogonal main effect plan (OMEP) will be used. In an OMEP design, all main effects are unrelated to each other and are optimal for main effects linear statistical models. The factorial model will consist of 2 alternative profiles with variations of the levels of each attribute, which will be blocked further into segments where the patient trade-off combinations of the attributes from a choice set. The combinations of the vignettes across the choice sets will be randomized and blocked.



Attribute	Medicine A	Medicine B
Mode of administration – how the medicine is taken	IV – An infusion given into the vein for a period of time	IV – An infusion given into the vein for a period of time
Dosing schedule – frequency of taking the medicine	One medicine taken by 30-minute infusion every 3 weeks	Two medicines, both are given as a 150-minute infusion every 3 weeks for 3 months (plus/minus: one of the two medicines are continued as 60-minute infusion every 2 weeks for 5 or more)
Median duration of therapy – how long the patient will be taking the medicine	8 months	8 months
Objective response rate (ORR) – how likely the cancer will respond to the medicine	33 out of 100 patients (33% chance of responding)	55 out of 100 patients (55% chance of responding)
Progression-free survival (PFS) – the average number of months before the cancer progresses although the patient is being treated with the medicine	5.5 months	14.0 months
Overall survival (OS) – the percentage of patients taking the medicine that are alive at 12 months	74 out of 100 patients (74% of patients survive to 12 months)	80 out of 100 patients (80% of patients survive to 12 months)
Likelihood that a patient will experience a side effect that requires hospitalization or medical intervention while taking the medicine	11 out of 100 patients (11% likelihood of experiencing a serious side effect)	55 out of 100 patients (55% likelihood of experiencing a serious side effect)
Select only one	**Medicine A**	**Medicine B**
If these were the only medicines available to you, which one would you choose?	❑	❑

Figure 3. An example of a DCE (Liu 2017) [28]

Time Trade Off (TTO)

The TTO method elicits preferences for health states by letting a patient imagine living a defined number of years in an imperfect health state. The patient then indicates the number of remaining life years in full health at which the respondent is indifferent between the longer period of impaired

4.1.2.4.

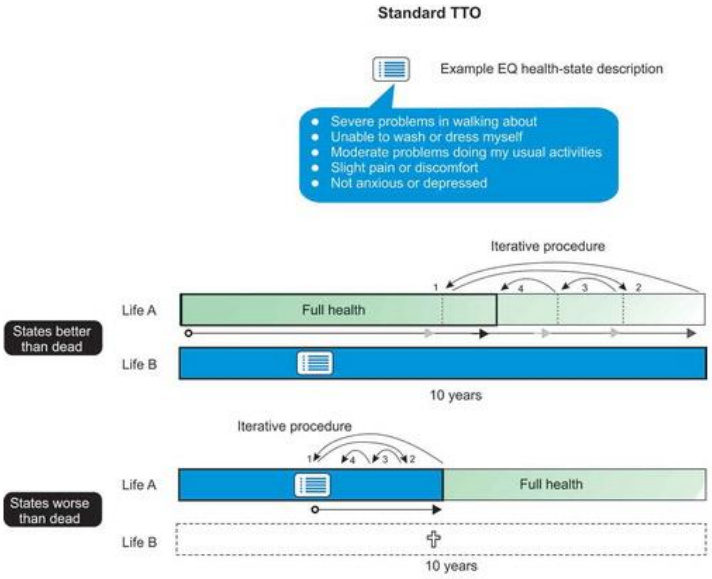


Figure 4. Example of the TTO methodology (Lugner & Krabbe, 2020) [29]

health and the shorter period of full health. This process is iterative, offering multiple lengths of life years to trade off before asking the respondent to select a point at which they are indifferent. The point at which a respondent is indifferent is then used to establish a value of the lesser state.[29] Normalizing the value of full health to 1.0 leaves us with the value of the impaired health state being represented by the ratio of the two periods, i.e., the number of years in full health divided by the number of years in the impaired health state.

The popularity of TTO specifications to achieve optimal health state valuation methods, in particular in the context HTA, which aim to inform policy makers in making resource allocation decisions in health care, have been criticised. There are variants of TTO producing different values for the same states,[30-31] and a lack of scientific standardization of TTO methods. Another challenge associated with TTO methods are the cognitive complexity required for the TTO task which may be difficult for certain patient populations to complete. The TTO procedure is criticized for problems associated with valuation of health states that are considered to be worse than

dead.[33-34] Not surprisingly, such perceived problems with TTO gave rise to a number of efforts to improve this method. Innovations in TTO are found in all elements related to the methods: new tasks, different procedures for data collection and different analytical strategies. It would be of interest to compare how preferences elicited from TTO methods compare to more popular methods like DCE in the context of regulatory decision-making. More specifically, TTO is a cardinal method (count data), rather than an ordinal method (ordering) like the DCE, so data from the TTO task will complement the DCE methodology by providing additional information to further understand the benefits and harms of novel drug therapies and the trade-offs patients make when making a treatment decision, such as information concerning the intensity and magnitude of how much patients prefer one attribute to another.

Multiple Criterion Decision Analyses (MCDA)

Multiple criteria or multicriteria decision analysis (MCDA) – also known as multiple criteria decision making (MCDM) – is the collective name of formal approaches that support decision making by taking into account multiple criteria in an explicit and transparent way.[35] The methodology of MCDA has extensively been used in various disciplines, but given their increased complexity as compared to other methods, they have not been as used in healthcare.[36] Swing weighting is a MCDA method and takes the criteria levels into account when estimating criteria weights. Patients are first exposed to a hypothetical worst-case scenario, where all attributes of preference are set to the worst possible levels.[37,38] They are then asked to identify the most important criterion to them by selecting the one that, if improved, would improve the overall situation the most. The most important criterion is assigned 100 points, and then decision-makers are asked about the next criterion to be moved from its worst level to its best – that will receive a point value <100.[39] Different options (e.g. treatments) are then scored against each criterion and the weights are used to summarize scores for the purposes of comparing these options.[40]

4.1.2.5.

4.1.2.6.

Variables

The web-based survey will include the following sections and variables:

- A DCE exercise to evaluate PP and estimate utilities;
- A short TTO exercise to evaluate health valuation utilities (subset of patients);
- A MCDA exercise to evaluate PP and estimate utilities (subset of patients);
- A ranking exercise in which respondents will be asked to rank order the attributes;
- A set of questions regarding:
  - Respondents' socio-demographics, clinical (.e. diagnosis, cancer stage, number of previous treatments), self-assessed health status, constructs related to choices that

may explain heterogeneity (i.e. age, disease severity, family background, patient's understanding of the disease, health awareness and literacy);
- Question to assess respondents' level of understanding of the DCE, MCDA/TTO tasks;
- Question to assess how difficult respondents found to complete the DCE, MCDA/TTO tasks

Sample

Study Eligibility Criteria

4.2.

Qualitative Evidence Generation

4.2.1.

- Patient is ≥ 18 years of age

4.2.1.1.

- Patient has a diagnosis of cancer
- Patient lives in a European country
- Patient has access to an internet browser or application to participate in the interview
- Patient can read and write in country-specific main language
- Patient can provide an email address and click on an invitation to participate in the interview
- Patient provides informed consent to take part in the study

4.2.1.2.

Quantitative Evidence Generation

- Patient is ≥ 18 years of age
- Patient has a diagnosis of cancer
- Patient lives in a European country
- Patient has access to an internet browser or application to complete the online survey
- Patient can read and write in country-specific main language
- Patient can provide an email address and click on an invitation to participate in the online survey
- Patient provides informed consent to take part in the study

Sample Size and Description

Qualitative Evidence Generation

Approximately 30 adult patients with cancer will be recruited to participate in the qualitative interviews for evidence generation of the attributes and review of the vignettes. In order to participate in this part of the study, patients must meet all of the eligibility criteria.

4.2.2.

4.2.2.1.

Quantitative Evidence Generation

Approximately 900 adult patients with cancer will be recruited to participate and complete a web-based preference survey to understand their treatment choices and treatment heterogeneity.

4.2.2.2. Sample size recommendations depend on the number of attributes and levels of each attribute included. Johnson and Orme [41, 42] suggest that the sample size required for assessing main effects depends on the number of choice tasks (*t*), number of alternatives (*a*) and the number of analysis cells (*c*) equal to the largest number of levels for any of the attributes: $N > 500c / (t \times a)$. Recently findings show that precision of preference estimates increase at sample sizes just below 150 respondents.[27] Most studies estimating PP include approximatively 100 – 250 respondents per country.[43] Given the number of attributes and the potential interactions to examine differences in task and heterogeneity, a larger sample size is warranted. We estimated the proposed sample size of approximately 900 patients will be sufficient to estimate preferences and to account for heterogeneity. In order to participate in this part of the study, patients must meet all of the eligibility criteria.

4.2.3.

Patient Recruitment

4.2.3.1.

Qualitative Evidence Generation

Approximately 30 adult patients with cancer will be recruited to participate in the qualitative interviews through patient panels. IQVIA will work with Global Perspective, our external patient recruitment partner, to recruit potential eligible patients to participate in the qualitative evidence generation phase of the study. The panel teams are from different sources, including marketing campaign targeting, social media, or through a referring process (such as by physicians or patients directly). Patients who would like to join the panel will be requested to complete a profiling survey where they will be asked several socio-demographic and healthcare questions so the panel can pre-target the patients as having a certain condition (e.g. NSCLC) and being part of a certain socio-demographic background.

Global Perspectives will invite potential eligible patients to participate in the qualitative evidence generation phase of the study. A screener will be developed by IQVIA to help identify eligible

patients, and confirmation of diagnosis will be obtained by Global Perspective using either a diagnosis prescription picture or a treatment prescription picture. Patients who are eligible based on the completion of the screener and agree to participate will be contacted to obtain electronic consent and will consequently have an interview scheduled.

Quantitative Evidence Generation

Approximately 900 adult patients with cancer will be recruited to participate in the quantitative phase of the study using a combination of both patient panels and patient advocacy groups (PAGs).

1.2.3.2

1. With the patient panel approach, IQVIA will work with Global Perspective to recruit potential eligible patients with cancer to participate in the quantitative phase of the study. Similar to the qualitative evidence generation phase, patients who would like to join the panel will be requested to complete a profiling survey where they will be asked several socio-demographic and healthcare questions so the panel can pre-target the patients as having a certain condition (e.g. NSCLC) and being part of a certain socio-demographic background. We propose a sample size of 300 patients with cancer recruited each from Spain (Western Europe) and Poland (Eastern Europe) (total = 600 patients) to have a better balance of different regions of Europe that may differ in terms of oncology treatment practices, and ensure heterogeneity in patients with cancer from different parts of Europe.

   Global Perspectives will invite potential eligible patients to participate in the qualitative and quantitative phases of the study. A screener will be developed by IQVIA to help identify eligible patients, and confirmation of diagnosis will be obtained by Global Perspective using either a diagnosis prescription picture or a treatment prescription picture. Patients who are eligible based on the completion of the screener and agree to participate will be sent a link via email to the survey. The anonymized data will be automatically saved to the data management platform.

2. Through the PAGs approach, IQVIA will work internally with our patient recruitment team to partner with EU PAGs to recruit potential eligible patients to participate in the quantitative study. We propose a sample size of 300 patients with cancer recruited from two European countries. This will be on a best effort basis and if 300 patients are not recruited, we will increase the recruitment using the patient panel approach. To further help supplement recruitment, the Agency will introduce IQVIA to the Agency's relevant PAG group, where IQVIA will then manage recruitment via patient panels. By utilising multiple recruitment strategies, we intent to minimize potential selection biases associated

with a single mode of recruitment and maximise the potential to make generalisable conclusions. The heterogeneity of the samples will lead to representative PP evidence for the European oncology patient population. The countries selected for the recruitment through Global Perspective will not be excluded from the recruitment strategy using PAGs.

Data Management

Qualitative Evidence Generation

4.3. For the qualitative phase, audio-recordings obtained during the patient interviews for will be transcribed into de-identified patient transcripts and translated in English. Audio-recordings be automatically deleted when transcription is completed. De-identified transcripts will be stored in an encrypted IQVIA server in a password-protected file, accessible only to specific study staff.

4.3.1.

Quantitative Evidence Generation

4.3.2. For the quantitative phase, eligible patients will be invited to participate and if interested, will complete an online consent, which will give them access to the PP survey. Patients will be requested to complete the choice sets, by indicating their preferred alternative for each scenario. The online platform where the data collected will be automatically stored, Qualtrics^{XM}, will allow for real-time review of the data for quality and completeness. Access to the database will be restricted with a username and password to key members of the research team.

Data will be validated as defined in the summarized Data Management Plan. Quality control procedures will be applied to ensure all the online data collected via the survey platform corresponds to the final survey and to eliminate potential missing, out of range, illogical or erroneous data.

A pilot phase will be conducted with 20 patients. Based on the feedback from the pilot-testing, modifications to the online survey will be made to finalize the electronic migration. No concurrent manual data review will be performed, and no queries will be followed up with patients for resolution.

High data quality standards will be maintained, and processes and procedures will be utilized to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. When all data have been validated, signed and locked, the data file will be declared as being a clean file. The final database will then be locked.

File Retention and Archiving

4.3.3. To enable evaluations and/or audits, all records, including source documents and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports) will be kept in IQVIA's secure servers. The records will be retained according to local regulations, or as specified in the study contract, whichever is longer.

All records will be kept and made available for review in the event of audits, or inspections and will be safely archived for at least 5 years after the completion of the study.

Monitoring and Reporting of AE / SAE

4.4. The sponsor will follow standard procedures for handling adverse events reporting involving these patients – specifically, reporting adverse events to drug safety.

In the event that the patient reports intent or actual harm to themselves or others, IQVIA will ask for the clinician contact during the interview and will report the incident to the patient's clinician or a local suicidal/crisis center to the best their capabilities.

5. Data Analysis

The sample for both phases will be described by means, standard deviations, median, and range, for continuous variables, and by number and proportion of the total study population for categorical ones.

5.1.

Qualitative Evidence Generation Analyses

To assess the face and content validity of the survey, vignettes, attributes and associated-levels, the data obtained from the interviews and the pilot will be assessed and coded thematically for analysis, and issues arising in relation to vignette content or format will be extracted and used for revision towards the final survey. Patient verbatim will be coded to examine comprehension, relevance, and ease or difficulty of selecting a response. The overall goal of coding these data is to facilitate the identification of concepts that are most important and relevant to patients. The coding process identifies and categorizes patient concept expressions. Coders review each transcript to identify text that includes concept expressions, and tags selected text with a code. The codes are organized within a coding framework, which is established at the beginning of the process and refined/expanded during the coding process. Once the coding process has been

completed, outputs are generated in tabular, graphical, or text formats to summarize results in WORD or PowerPoint reports. All interview transcripts (PDF format) will be included as appendices to the final report or in supplemental electronic files. Content within and between vignettes will be further compared and examined for comprehension and ease or difficulty of selecting a response.

For the qualitative phase, all data will be described using Atlas.ti® version 7 or higher and Microsoft® Excel.

Quantitative Evidence Generation Analyses

Primary Analysis

5.2.

5.2.1.

The final analyses will be fully described in the statistical analysis plan and will depend on the stated preference methodology used. Continuous variables will be described by mean, standard deviation (SD), 95% confidence intervals (CI), median, 25th and 75th percentiles, minimum and maximum. Categorical variables will be described by frequencies and related percentages of the study population, and by subgroups.

The primary objective is aimed at identifying and describing the cancer PP about benefits and harms of cancer drugs and to understand the trade-offs between factors leading to PP with the main method, DCE. For this objective, we propose using Bayesian multinomial logistic regression (MNL) models reporting odds ratio's and 95% confidence intervals. Attribute-levels will be estimated relative to a reference level for each attribute. The reference level will be selected based on the attribute-level having the lowest parameter estimate. The analysis of preferences of patients towards a treatment will allow us to investigate which attributes (and levels) influence patient choices for selecting the most appropriate treatment for patients with various cancers. A Bayesian MNL model computes the best fitting estimates via utility estimation to account for the overall pattern of choices reported by the patients. Results from utility estimation allows for the estimation of coefficients for each attribute-level, with a positive parameter in the model representing a positive utility associated with a particular attribute-level, whereas a negative parameter in the model represents disutility associated with a particular attribute-level. Using a Bayesian MNL model, the coefficients for the different attribute-levels can then be combined to allow for investigation of these factors when making a treatment decision.[41]

The relative importance of the attributes that are relevant to the patients' preference for selecting treatment will be also assessed depending of the stated preference method used. Generally,

mean part-worth utility values for each attribute will be estimated using the Bayesian MNL models for the main method DCE. Part-worths will be scaled and normalized to allow for comparisons to assess the relative importance of the attributes from most important to least important. The reference factor level will be set to the least important value for each attribute. The factor level with the largest part-worth (in absolute value) would also represent the impact of that attribute it belongs to.[45] The relative importance of the attributes will be described in related percentages.

To complement the analysis for this primary objective, cancer PP about the benefits and harms of cancer therapies and the different trade-offs between factors will also be examined using MCDA and TTO methodologies with a smaller subset of patients. For the MCDA method, partial value functions will be elicited using the additive value model. Ratings of the alternatives will be described, along with the sum of the preference weights to account for relative importance, using frequencies and related percentages. The sum and spread of the weights will be described using a non-linear curve representing the average weights as a function of the ratings. For the TTO method, regression analysis will be applied to estimate utility values by dividing the number of years corresponding to the patient's choices for a treatment by 10 (years). The patient's preferences with different treatments will be measured in units of quality of life differences between the two treatment options, and the utility values (mean, SD, 95% confidence intervals) will range between 0 and 1.

5.2.2. Secondary Analyses

5.2.2.1. *Secondary Analysis*

The secondary objective is to determine the extent to which patients' heterogeneous characteristics are associated with stated preferences. To explore variation in preferences for patient treatment based on patient factors collected (cultural characteristics, demographic characteristics, clinical (time of diagnosis, disease stage, treatment experience), psychological characteristics (cognition, health literacy, health numeracy, health attitudes); Bayesian MNL models will be conducted with coefficients for attribute-levels interacting with clinical variables (e.g. cancer type, level of experience) and socio-demographic variables (e.g. age, sex, country, education level) for the DCE methodology. Regression models will also be conducted to examine the relationship between the utilities from the MCDA and TTO methods and patients' characteristics, using regression coefficients and 95% confidence intervals. Regression assumptions will be assessed, and appropriate regressions models will be based on the assumptions and data distributions of the utilities.

Bayesian MNL models will also be used to control for differences in error variance and explore consistency of treatment choices for the DCE methodology. Random utility theory assumes that there may be an additional component of utility that is unobservable. Therefore, the utility function comprises of two elements: a deterministic component based on the participants' preferences for the observed attributes of the alternative, and random error associated with the alternative.[46] In the MNL model, it is assumed that choice questions measure utility equally well (or equally poor) across all participants and choice tasks. However, if the variance is not constant across all participants or choice tasks, differences in model estimates between participants or choice tasks may appear different and could lead to biased results. It is therefore important to control for error variances. Regression models will aim to be conducted to examine the relationship between the utilities from the MCDA and TTO methods and patients' understanding and differences when completing the choice tasks, using regression coefficients and 95% confidence intervals. Regression assumptions will be assessed, and appropriate regressions models will be based on the assumptions and data distributions of the utilities.

5.2.3. *Exploratory Analyses*

An additional objective is to compare and contrast preference weights and patient associations with stated preference using different stated preferences methods. Preference weights estimated from the three methods and association between preferences and patients' characteristics will be compared both descriptively and using anchor-based mapping regressions. Mapping predicts HRQoL states by statistically relating DCE scores to MCDA and TTO scores using a regression mapping method. The aim is for coefficients for each attribute to be calculated by multiplying the DCE coefficients by MCDA and TTO scores in separate regression models. The regression assumptions of the utilities for each method will first be examined and will aim to use appropriate models based on the assumptions and data distributions. Scatterplots of the residuals for the utilities from each method will be further examined. If the utilities violate assumptions and data distributions for regression, transformations may be considered. Otherwise, non-parametric techniques will be used.

Patients will also be asked about the level of difficulty completing each task (either DCE/MCDA or DCE/TTO). This question will be asked at the end of the survey, and the data will be compared descriptively. Continuous variables will be described by mean, standard deviation (SD), 95% confidence intervals (CI), median, 25th and 75th percentiles, minimum and maximum. Categorical

variables will be described by frequencies and related percentages of the study population, and by subgroups.

For the quantitative phase, all computations and generation of tables, listings and data for figures will be performed using Statistical Analysis System (SAS)® version 9.2 or higher (SAS Institute, Cary, NC, USA).

6. Storing and Archiving of Data

At the close of the study, all patient records will be archived in an access-controlled file for the period of 5 years from end of study.

7. Ethical and Regulatory Obligations

IRB Process & Informed Consent

7.1.

In accordance with local regulations and the ethical principles that have their origin in the principles of the Declaration of Helsinki, all patients must provide informed consent, or agreement to a data protection notice (DPN) before entering into the study. In the qualitative phase, all patients will be asked to provide verbal consent to participate in the interview. In the quantitative online survey phase, patients will provide their agreement to the DPN to be enrolled and continue with the online survey. Online consent or agreement to a DPN will be obtained prior to being granted access to the survey. Patients in either phase will be allowed sufficient time to consider participation in the study. By agreeing to the DPN, patients will consent to their data being used in the study unless they withdraw voluntarily afterwards for any reason.

In order to maintain patient confidentiality, patients in the qualitative interviews and the quantitative survey will be assigned a unique identifier upon study enrollment. This identifier will be used for the purpose of data analysis and reporting. All parties will ensure the protection of personal data and will not include names on any study forms, reports, publications, or in any other disclosures, except where required by law. Patients will be informed about data handling procedures and asked for their consent. Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data. Patient information will always be kept in a separate and encrypted database only accessible to the research team for the purposes of scheduling patient interviews. Every effort will be made to protect patient confidentiality according to the Directive 95/46/EC on the protection of individuals, and in compliance with Safe Harbor privacy principles.

Consistent with local regulations, a study protocol and patient facing material will be submitted to central Ethics Committees active in the countries of interest for its review.

Potential Risks and Limitations

7.2 There are no expected risks to patients as a result of involvement in this study. Their regular medical care will not change as a result of participating in this study and this study should not involve any physical risk.

There may be non-physical risks and limitations associated with taking part in different phases of the study, such as:

Qualitative Evidence Generation

7.2.1.
- Information bias: All data collected depends on patient report and recall. Self-reported preferences may also differ from observed or actual preferences. The IQVIA moderators will be fully trained on the study protocol, interview guide and good practice guidelines. Thematic coding of the transcripts will be recorded when patient verbatim is spontaneously reported or prompted.
- Selection bias: Generalizability is generally not sought in qualitative studies but rather recruitment of a diverse sample to provide varied insights. Efforts will be made to recruit a diverse sample of patients for the qualitative phase. Patient characteristics will also be fully described as per the patient screener.
- Burden to the patient: Reflecting on and trading off different treatment attributes of relevance may be overly cognitively burdensome to the patient. To minimize this risk, feedback on the qualitative interviews and identification of the attributes will be assessed using cognitive debriefing techniques.

7.2.2.

Quantitative Evidence Generation

- Information bias: As with collection of all self-report data, there is a possibility that patients may give inaccurate responses based on the method of survey administration. Using an anonymized online survey may reduce this type of bias compared to interview-based methods as risk of social desirability bias is minimized in the absence of a researcher, and in the knowledge that responses will not be linked back to individuals. This will be emphasized in the survey instructions to encourage accurate and truthful responses from

patients in this phase of the study. However, self-reported preferences may still differ from observed or actual preferences for reasons that cannot be controlled for in this study

- Selection bias: Study participation is voluntary, and the sample of patients recruited could differ those from the general population. Efforts will be made to ensure the recruitment of patients is as generalizable as possible. Information will be retained on patients not meeting selection criteria for enrollment. Patient characteristics will also be fully described as per the patient screener.
- Attributes identified and captured in the current study: There may be treatment attributes and factors outside of the current study that are important to patients but were not identified and represented in this study. There is also the risk that patients may not relate or understand certain attributes. Our attributes and associated-levels in the preference survey will be based on the targeted literature review and feedback received from patients during the qualitative evidence generation interviews. To minimize this risk, relative importance of attributes and associated-levels will be assessed. Patients will also be asked questions on how well the patients understood the attributes described in the choice tasks.
- Burden to the patient: The administration of the different PP methodologies and trading off different treatment attributes of relevance may be overly cognitively burdensome to the patient. To minimize this risk, patients will be informed how far they have completed the survey by including a progress bar in the survey.

7.3. Protection of Patients

7.3.1. Confidentiality

The privacy rights of individuals and the confidentiality of medical records will be protected in accordance with all applicable laws, regulations, and guidelines.

Sites and laboratories or entities providing support for this study, which process personal data relating to EU-based patients must comply with the EU General Data Protection Regulation in performing all their processing activities in connection with this study.

After patients have been informed about how their data will be processed and have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor

and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of patients' identities.

Patients are assigned a unique identifying number; however, their year of birth may also be used in combination with this number to assist the sponsor to verify the accuracy of the data (e.g., to confirm that laboratory results have been assigned to the correct patient).

The results of studies – containing patients' unique identifying number, relevant medical records, and possibly year of birth – will be recorded. They may be transferred to, and used in, other countries which may not provide the same level of protection that applies within the countries where this study is conducted. The purposes of any such transfer and use may include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities. The sponsor may transfer data collected in this study to its affiliates, collaborators, licensees and other companies and organizations working with or for the sponsor in connection with these purposes.

7.3.2. Potential Benefits

Potential benefits to patients with cancer include improved understanding of the benefits and risks of novel drug treatments for regulatory approval from the patient perspective and what patient, treatment and disease characteristics may influence treatment preferences for certain cancer types.

8. Intended Use of the Data

The data will be used to:

- Provide a better understanding of the experience of patients living with common and rare cancer types and what's important to patients, which ultimately could be used to design patient support interventions
- Identify and understand PP towards key endpoints used traditionally to assess efficacy and safety of oncology drugs, with implications for regulatory approval
- Provide a better understanding of the factors that influence cancer patient's treatment preferences about benefits and harms of cancer drugs

9. Documentation and reporting

A final study report will be generated after all data collection of the quantitative phase is complete. Following data collection and data analysis, a technical report detailing the objectives, methodology, results and interpretation/conclusions of the will be developed.

A plan for publication in a scientific journal will be determined with the Agency and will summarize the final study report. IQVIA will develop a scientific manuscript describing the methods and results of the PP study in people with cancer in Europe. IQVIA will prepare an outline of the paper and discuss this outline with the Agency. Based on the outline, IQVIA will construct one draft and one final version for review. After review, IQVIA will finalize the paper and submit the paper to a scientific journal (target journal to be agreed upon by the Agency and IQVIA).

10. Summary of Deliverables

Deliverables: PP study

1. Preliminary study plan/synopsis
2. a) Draft study protocol
   b) Final study protocol
   Registry of study in the EU PAS Register (http://www.encepp.eu/encepp/studiesDatabase.jsp)
3. Tools and material needed for the survey:

- Summary deck of literature review findings (PowerPoint)
- Conceptual model of treatment attributes (MS Word)
- Drafts (2) and a final Interview Guide (MS Word)
- Drafts (2) and final vignette and stated preference survey (MS Word)
- Drafts (2) and final Statistical Analysis Plan (MS Word)
- Drafts (2) and final Tables, Listings and Figures (MS World)

4. Final study report (MS Word)
5. Manuscript (MS Word)
6. Anonymized database

11. References

1. World Health Organisation. *Noncommunicable diseases*. 2018 1 June 2018 [cited 2020 14th October]; Available from: https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases.
2. Ferlay, J., et al., *Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018.* European Journal of Cancer, 2018. **103**: p. 356-387.
3. Bell, R., *Developing a Clinical Program Based on the Needs of Patients With Chronic Lymphocytic Leukemia: Preparing for Illness Episodes.* Journal of the advanced practitioner in oncology, 2017. **8**(5): p. 462-473.
4. Hardy, D., et al., *Chemotherapy-Associated Toxicity in a Large Cohort of Elderly Patients with Non-small Cell Lung Cancer.* Journal of Thoracic Oncology, 2010. **5**(1): p. 90-98.
5. Nardin, S., et al., *Breast Cancer Survivorship, Quality of Life, and Late Toxicities.* Frontiers in oncology, 2020. **10**: p. 864-864.
6. Escudier, B., et al., *Sorafenib in advanced clear-cell renal-cell carcinoma.* N Engl J Med, 2007. **356**(2): p. 125-34.
7. Sandler, A., et al., *Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer.* N Engl J Med, 2006. **355**(24): p. 2542-50.
8. Wong, Y.-N., et al., *Cancer patients' trade-offs among efficacy, toxicity, and out-of-pocket cost in the curative and noncurative setting.* Medical care, 2013. **51**(9): p. 838-845.
9. González, J.M., et al., *Patient and physician preferences for anticancer drugs for the treatment of metastatic colorectal cancer: a discrete-choice experiment.* Cancer management and research, 2017. **9**: p. 149-158.
10. Postmus, D., et al., *Individual Trade-Offs Between Possible Benefits and Risks of Cancer Treatments: Results from a Stated Preference Study with Patients with Multiple Myeloma.* Oncologist, 2018. **23**(1): p. 44-51.
11. Srinivas, S., et al., *Physician preferences for non-metastatic castration-resistant prostate cancer treatment.* BMC Urology, 2020. **20**(1): p. 73.
12. Shrestha, A., et al., *Quality of life versus length of life considerations in cancer patients: A systematic literature review.* Psychooncology, 2019. **28**(7): p. 1367-1380.
13. Brennan, P.F. and I. Strombom, *Improving health care by understanding patient preferences: the role of computer technology.* Journal of the American Medical Informatics Association : JAMIA, 1998. **5**(3): p. 257-262.
14. Hanley, N., Ryan, M., & Wright, R, *Estimating the monetary value of health care: lessons from environmental economics*. Vol. vol. 12, no. 1, pp. 3-16. 2003.
15. FDA (US Department of Health and Human Services FaDA, C.f.D.a.R.H.C., Center for Biologics Evaluation and Research (CBER),. *Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders: Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling (Draft)*. 2016; Available from: https://www.fda.gov/media/92593/download.
16. FDA (US Department of Health and Human Services FaDA, C.f.D.a.R.H.C., Center for Biologics Evaluation and Research (CBER),. *(Draft) Patient-Focused Drug Development: Methods to Identify What Is Important to Patients. Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders*. 2019; Available from: https://www.fda.gov/media/131230/download.

17. Postmus, D., et al., *Incorporating patient preferences into drug development and regulatory decision making: Results from a quantitative pilot study with cancer patients, carers, and regulators.* Clinical Pharmacology & Therapeutics, 2016. **99**(5): p. 548-554.
18. Trapero-Bertran, M., et al., *What attributes should be included in a discrete choice experiment related to health technologies? A systematic literature review.* PloS One, 2019. **14**(17): e0219905. https://doi.org/10.1371/journal.pone.0219905
19. de Bekker-Grob, E., et al., *Sample size requirements for discrete-choice experiments in healthcare: a practical guide.* Patient, 2015. **8:** p. 373-384.
20. De Brun, A., et al. *A novel design process for selection of attributes for inclusion in discrete choice experiments: case study exploring variation in clinical decision-making about thrombolysis in the treatment of acute ischaemic stroke.* BMC Health Services Research, 2018. **18**(483): p. 1-14.
21. Evans, S.C., et al., *Vignette methodologies for studying clinicians' decision-making: Validity, utility, and application in ICD-11 field studies.* Int J Clin Health Psychol, 2015. **15**(2): p. 160-170.
22. Patrick, D.L., et al., *Content validity--establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO good research practices task force report: part 1--eliciting concepts for a new PRO instrument.* Value Health, 2011. **14**(8): p. 967-77.
23. Patrick, D.L., et al., *Content validity--establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO Good Research Practices Task Force report: part 2--assessing respondent understanding.* Value Health, 2011. **14**(8): p. 978-88.
24. Bridges, J.F., et al., *Conjoint analysis applications in health--a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force.* Value Health, 2011. **14**(4): p. 403-13.
25. Soekhai V, W.C., Levitan B, Veldwijk J, Hammad T, Kihlbom U, et al. , *Compendium of methods for measuring patient preferences in medical treatment. .* Value Health, 2017. **20(9)**: p. A684–5.
26. Ryan, M. and S. Farrar, *Using conjoint analysis to elicit preferences for health care.* BMJ, 2000. **320**(7248): p. 1530.
27. Reed Johnson, F., et al., *Constructing Experimental Designs for Discrete-Choice Experiments: Report of the ISPOR Conjoint Analysis Experimental Design Good Research Practices Task Force.* Value in Health, 2013. **16**(1): p. 3-13.
28. Liu, F.X., et al., *Patient and oncologist preferences for attributes of treatments in advanced melanoma: a discrete choice experiment.* Patient preference and adherence, 2017. **11**: p. 1389-1399.
29. Lugnér, A.K. and P.F.M. Krabbe, *An overview of the time trade-off method: concept, foundation, and the evaluation of distorting factors in putting a value on health.* Expert Review of Pharmacoeconomics & Outcomes Research, 2020. **20**(4): p. 331-342.
30. Attema, A.E. and W.B. Brouwer, *Can we fix it? Yes we can! But what? A new test of procedural invariance in TTO-measurement.* Health Econ, 2008. **17**(7): p. 877-85.
31. Brazier, J., Ratcliffe, J., Salomon, J.A., Tsuchiya, A, *Measuring and Valuing Health Benefits for Economic Evaluation*. 2007: Oxford University Press
32. Bleichrodt, H., J.L. Pinto, and J.M. Abellan-Perpiñan, *A consistency test of the time trade-off.* J Health Econ, 2003. **22**(6): p. 1037-52.
33. Macran, S. and P. Kind, *"Death" and the valuation of health-related quality of life.* Med Care, 2001. **39**(3): p. 217-27.
34. Robinson, A. and A. Spencer, *Exploring challenges to TTO utilities: valuing states worse than dead.* Health Econ, 2006. **15**(4): p. 393-402.
35. Belton V, S.T., *Multiple Criteria Decision Analysis: An Integrated Approach*. 2002, MA, USA Springer Science & Business Media Boston,.

36. Marsh, K., et al., *Assessing the value of healthcare interventions using multi-criteria decision analysis: a review of the literature.* Pharmacoeconomics, 2014. **32**(4): p. 345-65.
37. Thokala, P., et al., *Multiple Criteria Decision Analysis for Health Care Decision Making—An Introduction: Report 1 of the ISPOR MCDA Emerging Good Practices Task Force.* Value in Health, 2016. **19**(1): p. 1-13.
38. von Winterfeldt D, E.W., *Decision Analysis and Behavioral Research* 1993, Cambridge, UK: Cambridge University Press.
39. Sullivan, T. *Using MCDA (Multi-Criteria Decision Analysis) to prioritise publicly-funded health care*. 2012.
40. York Health Economics Consortium. *Multi-Criteria Decision Analysis (MCDA) [online]*. 2016 [cited 2020 14th October]; Available from: https://yhec.co.uk/glossary/multi-criteria-decision-analysis-mcda/.
41. Johnson, R. and B. Orme, *Getting the most from CBC.* Sequim: Sawtooth Software Research Paper Series, Sawtooth Software, 2003.
42. Orme, B., *Sample size issues for conjoint analysis studies.* Sawthooth Software Research paper Series Squim, WA, USA: Sawthooth Software Inc, 1998. **10**.
43. de Bekker-Grob, E.W., et al., *Sample Size Requirements for Discrete-Choice Experiments in Healthcare: a Practical Guide.* The patient, 2015. **8**(5): p. 373-384.
44. Louviere, J.J., D.A. Hensher, and J.D. Swait, *Stated choice methods: analysis and applications*. 2000: Cambridge university press.
45. Kuhfeld, W.F. *Marketing research methods in SAS: experimental design, choice, conjoint, and graphical techniques*. in *SAS Document TS-694.< http://support. sas. com/techsup/technote/ts694. pdf>. Accessed on March 2*. 2007. Citeseer.
46. Vass, C.M. and K. Payne, *Using Discrete Choice Experiments to Inform the Benefit-Risk Assessment of Medicines: Are We Ready Yet?* Pharmacoeconomics, 2017. **35**(9): p. 859-866.