Submission of comments on 'IMI PREFER' (53468)

Comments from:

Name of organisation or individual
1. Clinigma
2. IQVIA Laurie Batchelder, Scientific Manager, Patient-Centered Solutions, IQVIA Ana Maria Rodriguez, Director, Patient-Centered Solutions, IQVIA Matthew Reaney, Senior Director, Patient-Centered Solutions, IQVIA Mary New, Senior Principal, Patient-Centered Solutions, IQVIA
3. EFPIA
4. JDRF
5. EuropaBio

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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General summary of points	Clinigma	1. While well written, the documents miss a major focus on eliciting the patient voice in PPS. 2. The abstraction of the document at times moves away from the key message of listening to patient experience. The evidence should be as close as possible to the immediate patient experience. This may not always be well reflected by complex trade-off techniques. 3. Lack of appreciation of the value of open-ended questions in capturing patient preference data. By interviewing trial patients about their experiences with the investigational drug, it is possible to gather early insights on how the patients experience the benefits and risks of the new drug, and if they see them as meaningful or not. This type of feedback can help with an earlier clarification of if the description of the benefits and risks are correctly described - thereby ensuring that the preference study has a correct and valid description of the new drug. 4. Limited list of methods: over-focused on complex weighting schemes which have been generally intended for use by fairly	Acknowledged, with the following remarks: Lack of patient focus is not agreed; the methods listed are non-exhaustive and described as such; there is little reason to see risk of misperceiving the framework as guiding away from (mainly) qualitative work, depending on the specific setting or use case; Lines 80-88 of the 'Opinion' address potential use scenarios and respective timing (also in relation to clinical studies) can be derived. Prospective and post-hoc approaches for PPS are stated. Overall, no action taken based on this general summary. With regard to the subsequent section providing comments on the IMI 'Framework' document please note that the 'Framework' document as such is not to be amended. Upon review, no changes to the 'Opinion' were deemed necessary based on the comments provided. Regarding specific comments on the 'Opinion' text (and respective outcome), please see further below.

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		quantitative 'experts' and could pose excessive burdens on patients. The time burden of these methods should be taken more explicitly into account. 5. Lack of discussion on timing of patient preference interviews. ********** 1. While acknowledging the utility of tools such as discrete choice experiments (DCE) and best-worst scenarios (BWS), patients can speak from their own experience in their own words as part of fit-for-purpose preference studies. This is acknowledged in the 'Patient Centricity' principle for interaction with patients in section 2.4.2 of the draft guidance, but could be a stronger theme throughout. The validity of the preference studies firmly depends on how the benefits and risks have been assessed. If they have only been described by "experts" at the early stage of the drug development, where the understanding of the drug is limited with large confidence intervals around the effects - and not been assessed by trial patients who have experienced the benefits and risks of the investigational drug itself - there is likelihood that the preference studies may not give a	

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		correct picture of the patients preferences of the attributes of the new drug. Clinigma strongly recommends to involving patients participating in clinical trials in patient preference studies, as this will overcome many of the practical issues with recruiting patients with the relevant profile and countries of interest. 2. Patients are experts in assessing the benefit and risks of their disease or condition (and how the symptoms and the treatment(s) impact their daily lives from their own experience. They are the ultimate stakeholders in the outcomes of medical treatment. Patients are also experts in how their disease and the treatment impacts their daily lives, as well as the extent to which they experience the novel treatment as meaningful. According to the 2021 FDA Benefit-Risk Assessment for New Drug and Biological Products Guidance for Industry, patient experience data can inform nearly every aspect of FDA's benefit-risk assessment throughout the drug lifecycle, including: • Therapeutic context, such as: ○ Impact of the disease and its treatment on the patient	

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		○ Patients' perspectives about available treatments and unmet medical needs ○ o Enhanced understanding of the natural history of the disease or condition, including progression, everity, chronicity • Potential benefits that are most meaningful • Acceptability of risk and uncertainty • Value and burden of risk mitigation efforts 3. The ways in which benefits and risks are presented are supposed to be objective, but if you do not know how the drug works on the effects and side effects of the treatment from the patient's own experience it is hard to present the findings objectively. * With rating and ranking exercises, because respondents are not forced to make trade-offs, there is no motivation to think about the relative importance and this results in a tendency towards rating everything as important. A more fundamental problem is that ratings assume utility to be a cardinal construct. * Non-engagement can also be a problem if measures take patients more than 10 minutes to complete. There is also a significant cognitive burden associated with methods such	

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		as ranking, choice-based methods (such as DCEs), trade-offs and best-worst scaling methods. * If you want a better understanding of objective descriptions of side effects, then you need to ask the patients who have used it. This process is key for drug development. To build stronger benefit risk assessment studies, it is therefore important to incorporate early user feedback e.g. trial patients, caregivers investigators and study nurses to strengthen the description of the benefits and risks that patients experience when using the new investigational drug. 4. In the PREFER framework components of 1) defining the preference study purpose and objectives, and 2) planning, designing and conducting the preference study, the patient perspective needs to be at the forefront if the study is going to be a strong objective presentation. It is those patients who have tried the drug who can describe in what way they experience the effects and side effects. * The qualification package for the PREFER framework presents five methods for eliciting preferences: discrete choice experiment, two types of best-worst scaling, threshold	

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		technique, and swing weighting. PRO outcomes are often scores or scales which can be difficult to interpret without an explanation from the users. Example: Clinigma once used a large generic health Outcomes questionnaire in a clinical trial on a product which was somewhat the same as the comparator, but with some improvement. When we got the PRO results, we could see that there was an improvement in one of the sub-domains (less moderate pain). The problem was because we did not interview the patients after they had participated in the trial, it was not possible to explain what this was due to. Was it because of the medication? Or the needle that was used? We did not know. So, when the results were presented to Regulatory and in HTA dialogues, we could not provide an answer to the very relevant questions from the institutions – why was this change in the PRO score seen in the trial? PRO may thus provide good scores and scales, but they may need an explanation – which patient experience interviews can offer an answer to through open-ended questions. 5. Always be clear about at which point in the trial the patient preference interviews will take	

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		place (pre, during, at exit). Patient's assessment of their preferences are at their strongest when patients have experienced the treatment (during or at-exit) – less so if they have not been exposed to the treatment.	
Section 1.1 (pg.16)	Clinigma	Comment: Further detail could be added to discussion of patient preference studies in the problem statement – sentence "*This is particularly the case in decision-making contexts that are sensitive to the preference of the patient (see Section 2.1), called patient preference-sensitive decisions."* Proposed change (if any): Add text below into problem statement section 1.1. '*Patient preference studies are dependant on an objective, correct and full description of the benefits and risks that are associated to a new drug. The challenge is, that this is rarely the case in drug development, where in particular in the early phase of the drug development there is high uncertainty of how the drug works. Very often key endpoints are associated with large confidence intervals. The key endpoints in product profile are not a guarantee for a complete list of the effects of the drug. Thus, there may be other benefits or drawbacks of the drug that may or may not be*	With regard to this section providing comments on the IMI 'Framework' document please note that the 'Framework' document as such is not to be amended. Upon review, no changes to the 'Opinion' were deemed necessary based on these comments. Regarding specific comments on the 'Opinion' text (and respective outcomes), please see further below.

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		identified later in the drug development. The drawbacks are more prone to be identified through the AE processes in the trial - but the full value the drug brings to patients may not be known - as the way benefits are assessed in clinical trials are through prespecified endpoints and PROs in RCTs. The fundamental challenge is that this approach only give answers to the questions asked - not a guarantee of the full picture of the benefits. Also, there may be a presumption that a certain treatment effect will be beneficial to the patients. But without having listened to the early users e.g. the trial patients who have tried the investigational drug and how it impact their lives - it can be hard to describe the benefits and drawbacks/risks in full of the drug. When the description of the benefits and risks may not be correct - this will also impact the validity of the outcomes of the preference studies. *To build stronger benefit risk assessment studies, it is important to incorporate early user feedback e.g. trial patients, caregivers investigators and study nurses to strengthen the description of the benefits and risks that*	

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		patients experience when using the new investigational drug'.	
Section 1.1 (pg.16)	Clinigma	Comment: Addition of phrase suggested for sentence. Proposed change (if any): to add 'or treatment attribute' to sentence '*In essence, in certain situations decision-makers may feel the need to better understand what matters to patients (e.g. what their primary needs are or what clinical endpoints are important to them)*'.	See above.
Section 1.1 (pg.16)	Clinigma	Comment: Addition of bullet point to stakeholders main concerns. Proposed change (if any): Addition of bullet point to stakeholders main concerns: *'Lack of complete picture of the benefits and risks of new investigational drugs and what the benefits and drawbacks/risks mean to the patients. Without the input from trial patients on how they experience the benefits and risks - it can be hard to make a complete description of the benefits and risks - which can impact the validity of the preference studies'.*	See above.
Section 1.4 (pg.17)	Clinigma	Proposed change (if any): consider adding '*with the investigational drug'* to end of '*the main objective of the PREFER framework is to offer a tool to support the inclusion of patients' views'*	See above.

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		And add: '*as they often hold experiences with other treatments (also due to trial design e.g. Rituxan Hycaela cross over trial design) - and too can benefit from better treatments of the patients'* to end of sentence '*While HCP preferences can certainly add an important and potentially different perspective'*.	
Section 2.1 (pg.22)	Clinigma	Proposed change (if any): consider adding bullet for importance of knowing more about following scenarios: '*How valid are the description of the attributes of an assessment? With new investigational drugs it can be hard to know exactly how the drugs are experienced by the patients. If the description of all the attributes is not a correct reflection of how the patients experience them - it can jeopardize the validity of the preference study. By interviewing the trial patients about their experiences with investigational drugs about the attributes of the drug - it can be clarified be the users how they see a correct description of an attribute should look - and if the attributes are viewed as a positive benefit or a negative effect/risk'*	See above.
Section 2.1 (pg.22)	Clinigma	Comment on '*What matters to patients'* bullet point:	See above.

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		Patients may respond differently to what matters to them - depending on if they have been exposed to the treatment or not. E.g. If RA patients have not exposed to the new treatment in question - e.g. a new painkiller it can be hard for them to correctly assess the importance of the pain relief – E.g. less pain - but where?, how much? and how long..?. how the pain relief is experienced by the patients matters to assess correctly if the pain relief attribute actually matters to the patients or not!	
Section 2.1 (pg.22)	Clinigma	Proposed change: consider adding additional bullet point to 'The acceptability of trade-offs': '*Trial patients may have had their disease for some time - and thus may have been exposed to current standard of care. In this situation trial patients can be asked to assess the attributes of the investigational drug vs. their previous treatment. And patients can elaborate on how they experience the difference - and how it impact their daily living*.'	See above.
Section 2.1 (pg.21)	Clinigma	Comment: Additional detail might usefully be added to situations when preference data is likely to be useful. Proposed change (if any): Additional detail below to potentially add to section 2.1	See above.

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		'Situations when patient preference data are most likely to be useful to support decision-making (patient preference sensitive decisions)'. *QoL questions might not capture all factors that are important to patients, providers or policymakers, such as non-health outcomes or process characteristics.* *Patient preferences for treatment outcomes, also play an important role in clinical trials when choosing between different treatment options. Preferences may also have an influence on trial outcomes.*	
Section 2.1 (pg. 22)	Clinigma	Comment: An additional scenario of how patients weigh benefits versus risks/harm would be useful to include. When balancing the benefits and risks patients have experienced with the treatment, it is important to explore what patients feel is important to tell other patients. Proposed change (if any): Consider adding additional bullet point under *'The acceptability of trade-offs'*: * Acceptability of risks to obtain benefits. Thinking about a patient's experience of the drug, if they were shown a predicted impact of this drug, for example a 90% increase in	See above.

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		likelihood of an event, or an increase in life expectancy, would this change their views on the drug or preferences towards the treatment?	
Section 2.2.1.1 (pg.23)	Clinigma	Comment on opening sentence: The problem remains: In the early phase of the drug development there is limited understanding of how the drug works - in particular within rare diseases. Asking patients may about attributes that would matter to them may not reflect the actual drug - thus the preference study at that early timepoint can be misleading. E.g. if pain relief is not working where the RA patients would hope it worked.	See above.
Section 2.2.1.1 (pg.24)	Clinigma	Comment on section heading '*Understanding patient's views on non-health benefits'*: Patient preferences may differ depending on if patients have been presented to only - or if they have experienced the benefits/non-health benefits. Clinigma had such case, where patient had placed a benefit of reducing a clinical adverse event was most important benefit of a new drug - but it turned out that once it was on the market, where patients could speak from their experiences with the treatment, that patients placed a higher	See above.

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		appreciation on the higher flexibility in their treatment.	
Section 2.2.2 (pg.24)	Clinigma	Comment: The problem is that with investigational drugs in development, is that the benefits and risks are not well known - which is why the drugs are being tested in clinical trials. The endpoints and risks may be identified in the trials - but what they mean to the patients, and how they impact their daily lives is not firmly captured in the trials. This evidence is often captured outside of a clinical trial - but asking patients about their appreciation of a benefit or a risk they read on paper - is not the same as having experienced it themselves - just like sex.	See above.
Section 2.2.1.2 (pg.24)	Clinigma	Comment: A further example could be useful under section 2.2.1.2 heading 'Understanding patients' views on non-health benefits'. Proposed change (if any): Could add another example here regarding overall benefits of the treatment versus any anticipated costs (these costs could be financial or opportunity costs)	See above.
Section 2.2.2 (pg.25)	Clinigma	Comment on '*How choice of patient-relevant endpoints can inform regulatory decision-making'* sub section: Patient preferences may change as more information of the drug (and what it means to	See above.

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		the patients) may be captured in the clinical trials until seeking marketing authorization. If insights about what the patients think of the investigational drug are not captured, there is a risk that early preference studies (where there is little knowledge of how the drug works) may not reflect what patient think of the drug and its attributes once it is on the market.	
Section 2.2.3 (pg.29)	Clinigma	Comment on '*Understanding patients' views on acceptability of benefit-risk trade-offs, acceptability of uncertainty'* section first paragraph: The validity of the preference studies firmly depends on how the benefits and risks have been assessed. If they have only been described by "experts" at the early stage of the drug development, where the understanding of the drug is limited with large confidence intervals around the effects - and not been assessed by trial patients who have experienced the benefits and risks of the investigational drug itself - there is likelihood that the preference studies may not give a correct picture of the patients preferences of the attributes of the new drug.	See above.

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Section 2.3 (pg.31)	Clinigma	Comment on Jensen et al., (2019) quote at the end of first paragraph in section: And when it is possible to know how the drug actually works in patients. This is not possible at early stage of the new drug development, where the drug is tested for safety only - and where the uncertainty is high on the primary and secondary endpoints - and not knowing if the drug has additional benefits.	See above.
Section 2.3 (pg.32)	Clinigma	Comment on Figure 2-3: There may be a presumption that what is relevant for patient on a new treatment can be assessed by experts or patients who have not tried the new treatment. The fallacy of this argument is the same as assuming that "all swans are white". This is not the case, as we all know. New drugs bring per definition improvement to the treatment on some of the benefits - and even a formulation may have much larger/less impacts on the patients' lives which only the users can explain after having used the new treatment. Patient assessments of how they experience the benefits the risks of the new treatment can provide a re-assurance that the new drug is not overlooking/overestimating the value of a new treatment.	See above.

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Section 2.4.2 (pg. 33)	Clinigma	Comment: Could incorporate importance of trained and experienced researchers carrying out the interviews as an additional principle for interaction with patients. Proposed change (if any): This could be incorporated under principle 6 '*Well prepared'*.	See above.
Section 2.4.4 (pg.39)	Clinigma	Proposed change: consider adding below to key considerations in first paragraph: including '*a sufficient and representative sample of patients who participates in relevant clinical trials - who could participate in the "typical" preference study around screening of the trial - AND also be interviewed at the exit of the trial - where patients can have an ability to elaborate on if their assessment of the benefits and risks has changed as a consequence of having tried the investigational drug*.'	See above.
Section 2.5.3 (pg.43)	Clinigma	Proposed change: consider adding below to '*In summary, the context of the use of the results is critical'*. '*As previously mentioned, it is important to emphasize the knowledge of the new investigational drug and how it is experienced the patients can be quite limited in particular at early stage of the drug development. What is viewed by patients as relevant endpoints*	See above.

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		depend on their current situation - which may change as a consequence of the new treatment. If patient have not experienced the benefits and risks of the new treatment - their assessment may not be a correct - which can lead to wrong conclusions.'	
Section 3.1.1 (pg.45)	Clinigma	Proposed change: consider adding to last bullet point 'A qualitative study could be done in isolation': '*..and elaborate in what way the attributes impact patients lives*.'	See above.
Section 3.1.2.3 (pg.48)	Clinigma	Proposed change: consider adding '*and over the course of a treatment and as a consequence of the treatment*..' to sentence '*An individual's preferences may change over time…*'	See above.
Section 3.2.1 (pg.51)	Clinigma	Proposed change: consider adding the below to the following sentence: '*Different decision-makers can, of course, have different views on which other treatment options are relevant to their decision'* '*Pharma companies may have their preferred comparators - where HTAs have theirs. If possible, it could be relevant to ask clinical experts and doctors in the countries of interest - who are used to treating patients with existing treatments*.'	See above.

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Section 3.2.1 (pg.52)	Clinigma	Comment on b) Description of how this decision is preference-sensitive i: which issues that are important to patients depends on the patients' situation including the treatment they experience.	See above.
Section 3.3.1.1 (pg.53)	Clinigma	Comment on first bullet point under *'Expected areas of expertise'*: Preferably to also include patients who have had experiences with the treatment. This could be trial patients who have tried the investigational drug and thus experienced the benefits and risks of the new treatment - and who can help make a more correct description of the benefits and risks than patients or experts who have not tried the new drug.	See above.
Section 3.3.1.1 (pg.54)	Clinigma	Comment on last bullet point 'patient engagement': Preferably to also include patients who have had experiences with the treatment. This could be trial patients who have tried the investigational drug and thus experienced the benefits and risks of the new treatment - and who can help make a more correct description of the benefits and risks than patients or experts who have not tried the new drug. Comment on end of first paragraph *'(e.g. if several industry partners have a common*	See above.

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		interest in understanding which are the most patient-relevant endpoints in a particular disease area).' It is important to make sure of that the endpoints are relevant for the patients within the specific disease AND also to make sure of that the endpoints are also relevant for investigational drug in focus - e.g. even a changed formulation can have a large impact on the patients lives - e.g. subcutaneous injections taking at home instead of IV. injections at the hospital.	
Section 3.3.1.2 (pg.55)	Clinigma	Comment on end of first paragraph 'the timing should also be aligned with an appropriate level of knowledge about the associated medical product. For example': That is correct - The knowledge about the drug is typically very limited at early stages of the drug development. The early clinical trials are designed to assess the safety of the drug - not efficacy - thus important understanding of the efficacy of the drug is not typically assessed before in the pivotal clinical trials - typically after 3A and 3B. This itself can impact the ability to make a correct description of the safety and efficacy profile of the new drug. One thing is getting an understanding of the safety	See above.

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		and effects of the drug from the trial - another is to understand in what way the effects and risks are meaningful to the patients or not. Patients who struggle with pain - and have not tried the drug may assess that e.g. product that provides a reduction in pain has an important benefit to them. But if the reduction in the pain is not experienced by the patients as relevant – e.g. because the pain reduction works in areas of the body that are not most important to most of the patients - or the pain reductions comes at a time point where they do not need it then it can impact the correctness of the preference study. By interviewing patients about their experiences with the investigational drug, patients can elaborate on how they experience the treatment and in what way they experience the treatment outcomes and risks as relevant and meaningful. This important insight can help the design of a stronger preference study. Comment on first bullet point: The problem is that the results about the new drugs comes in different trials - the safety is assessed in early stages of the drug development - where the efficacy - how well the drug works - is identified in the later	

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		stages of the drug development - in phase 3a and 3b trials. As stated before using patient interviews in relation to clinical trials can help provide an understanding of in what way the patients experience the new treatment effects and side effects as meaningful and how the treatment impact the patients daily lives. This type of insight can help overcome the challenges of lack of understanding of how the treatment effects of the new drug is relevant or not to the patient. Comment on final paragraph '*additionally, a development program could include…*': Bravo! We agree with this. The trial patients experiences of the investigational drug may help a correct assessment of the benefit-risk trade-offs - as they have tried the investigational drug - and have experienced how/if the effects and side effects impacted their lives or that they did not. Also preference studies can be conducted in relation to the clinical trials. The is shown in the Retuxan Hyceala study case where 77% patients express their preferences for the new formulation.	
Section 3.3.1.2 (pg.56)	Clinigma	Proposed change: consider adding additional bullet point to '*Operational considerations'*	See above.

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		'*The time where strong data about the new drug effect and risks are available without large uncertainties/confidence intervals*.'	
Section 3.3.2.2 (pg.57)	Clinigma	Proposed change: consider adding below to end of '*Alignment of the preference study population with the study preference study purpose'*: '*Patients who are enrolled in clinical trials, are often recruited to support a labelling claim where the drug is intended to be used, why it can be useful to conduct preference studies among these patients - also because in particular within rare diseases, where it can be hard to recruit patients*.' Comment on '*Consideration of the representativeness of the preference study sample for the target population of the medical product'* bullet point: Preference studies may not represent the target population: Also, it may turn out that the drug is most effective in a certain sub-population, where it is eventually gets authorization. This support to interview the trial patients as early as possible to get faster feedback on how the users of the drug experience the benefits and risks - and use this insight in the preference studies.	See above.

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Section 3.3.2.2 (pg.58)	Clinigma	Comment on end of first paragraph '*recruitment through a variety of routes'*: e.g. interview trial patients participating in global clinical trials in different countries. Proposed change: consider adding below to final paragraph '*Including patients from multiple countries…*' '*This can be solved by conducting the preference study in relation to a global clinical trial, where the trial patients can reveal their preferences. As also shown in table 3-7 below, this was done in Rituximab - where patients had been exposed to the treatment and could reveal their preferences. This got into a labelling claim with the FDA.*'	See above.
Section 3.3.2.2 (pg.59)	Clinigma	Comment on bullet point '*The preference study population can be recruited from a clinical trial (and hence defined in the same way for the clinical trial population*)': Correct! listen to the patients who have actually used the drugs and have experienced how the treatment was meaningful or not.	See above.
Section 3.3.2.2 (pg.59) Table 3-8	Clinigma	*Comments on 'Within clinical trial' column in Table 3-8:* *PROS*	See above.

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		- 'Straightforward to ensure alignment between preference study population and clinical trial population.' That is speculation - it can be done in a cost-effective way. *- Proposed change: add bullet on Operational benefits:* *'It is much cheaper to conduct preference studies in relation to a clinical trial than outside of a clinical trial, as it can reduce the costs that are associated to writing a separate protocol, seeking EC/IRB approval, recruiting patients with the right profile where the drug is intended, recruiting clinical, contracting with patients and sites, organizing and executing the study - it is much easier and cheaper to do it relation to a clinical trial where the whole organisation, PV process have been set up, and clinical sites are set up and trained already. Also, this opens up for that preference studies can be replicated in later clinical trials - which is also correctly suggested - because the knowledge of the drug increases throughout the drug development, and the drug may come in another formulation/concentration in the later trials compared to the first PK/PD studies in the early trials. It is much easier and so*	

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		much cheaper to do preference studies in relation to a clinical trial!' *CONS* *- 'Patients within clinical trials are not likely to be representative of the broader patient population.'* Propose to add...*'but more relevant for the target group where the drug is intended to be used.'* *- 'Patients within a clinical trial may be less risk adverse compared to the overall patient population'* This is speculation. Propose to delete - Propose to add to Operational issues bullet: '*Pre-testing of the components can be done in prior clinical trials, where patients who have experienced the drug can challenge the comment the descriptions'*. - '*It can be more expensive to do the preference study within the clinical trial'.* That is speculation, propose to delete. It is much cheaper to conduct preference studies in relation to a clinical trial, as it can reduce the costs that are associated to writing a separate protocol, seeking EC/IRB approval, recruiting patients with the right profile where the drug is intended, organizing and executing the study -	

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		it is much easier and cheaper to do it relation to a clinical trial. Also this opens up for that preference studies can be replicated in later clinical trials - which is also correctly suggested - because the knowledge of the drug increases throughout the drug development, and the drug may come in another formulation/concentration in the later trials compared to the first PK/PD studies in the early trials.	
Section 3.3.2.3 (pg.63)	Clinigma	Proposed change to add: '*and semi-structured interview manuals'* to 'a. approaches for developing descriptions of alternatives'.	See above.
Section 3.3.2.5 (pg. 65)	Clinigma	Propose change to add below to bullet point '*Patient Education and comprehension*': '*(including example exercise or trial patients with practical experiences with the new treatment*)' Comment: there is a double sentence at the beginning of 'Description of alternatives' section Proposed addition to end of this paragraph at top of page 66: '*As mentioned before, the problem is that at early stage of the drug development there is limited insight in how the drug works - there is a presumption but is that correct? The*	See above.

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
		expected benefits have large confidence intervals - but is the list complete? That is hard to tell. The early clinical trials give answers to safety questions - not efficacy questions - thus the knowledge of how the drug works in patients is still limited in the early stage of the drug development. At later stages - the efficacy trials reveal how the drug works for the patients. The challenge that knowing what is most important to the patients when using this new drug... By interviewing trial patients you can get an early feedback from trial patient - who have actually tried the drug and experienced the effects of the drug and how it impacted their daily living, which can help inform the description for the planned preference study - as they are the first ones who are able to tell what is most important to them when using the drug'.	
Section 3.3.2.5 (pg.66)	Clinigma	Comment on 'Top-down' bullet point: As mentioned before, the problem is that at early stage of the drug development there is limited insight in how the drug works - there is a presumption but is that correct? The expected benefits have large confidence intervals - but is the list complete? That is hard to tell. The early clinical trials give answers to	See above.

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
		safety questions - not efficacy questions - thus the knowledge of how the drug works in patients is still limited in the early stage of the drug development. At later stage - the efficacy trials reveals how the drug works for the patients. The challenge that knowing what is most important to the patients when using this new drug... By interviewing trial patients you can get an early feedback from trial patient - who have actually tried the drug and experienced the effects of the drug and how it impacted their daily living, which can help inform the description for the planned preference study - as they are the first ones who are able to tell what is most important to them when using the drug.	
Section 3.3.2.5 (pg.68)	Clinigma	Comment on 'Internal validity assessments(s) paragraph, sentence *'addressing issues of internal validity'*: A validation of the description of the treatment alternatives should be made also. As mentioned before, the problem is that at early stage of the drug development there is limited insight in how the drug works - there is a presumption but is that correct? The expected benefits have large confidence intervals - but is the list complete? That is hard to tell. The early	See above.

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
		clinical trials give answers to safety questions - not efficacy questions - thus the knowledge of how the drug works in patients is still limited in the early stage of the drug development. At later stage - the efficacy trials reveal how the drug works for the patients. The challenge that knowing what is most important to the patients when using this new drug... By interviewing trial patients you can get an early feedback from trial patient - who have actually tried the drug and experienced the effects of the drug and how it impacted their daily living, which can help inform the description for the planned preference study - as they are the first ones who are able to tell what is most important to them when using the drug.	
Section 3.3.2.5 (pg.73)	Clinigma	Comment on first sentence of '*Assessment of study material(s)'* heading: Such assessment could be made in relation to a clinical trial, where trial patients who have been exposed to the trial drug can challenge and assess the study material based on their experiences they have had with the investigational drug.	See above.
Section 3.3.3.2 (pg.75)	Clinigma	Comment on first sentence under heading: It can be quite a challenge, require a lot of time and can be very costly - also because it	See above.

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
		requires contracting with personnel, PV process and training, separate contracting with patients who can be very hard to recruit - in particular within rare diseases. This is also why it is recommendable to use the opportunity to invite trial patients who are to participate in a planned clinical trial to participate in a preference study.	
Section 3.3.3.3 (pg.75)	Clinigma	Comment on second bullet point under '*Data collection will be required for'*: The data about the patients can require a control to be sure of that the respondents are who they are - which can be quite cumbersome and costly. If the patients are recruited in relation to a clinical trial - the control of the patient and their characteristics is done by the clinical sites - ensuring the important validity of the patient characteristics. Comment on bullet point under '*Considerations with respect to interpreting study results'* (pg. 76)*:* Saturation is not necessarily the point in qualitative studies - as it can be equally important to find out the reasons to the differences in the responses - e.g. patients with more severe vs. less disease, older patients vs. younger patients...	See above.

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Section 3.4.3.4 (pg.104)	Clinigma	Comment: Why only including health-related quality of life in '*In particular for HTA, an additional assessment element on patient preferences could be added to the HTA Core Model (https://eunethta.eu/hta-core-model/) in the clinical effectiveness domain. This domain currently includes assessment elements such as impact of the intervention on health-related quality of life*.' PPS can also add value to non HRQoL impacts on daily living such as familial and peer relationships, intimate relationships, performance of work/voluntary roles, and participation in hobbies/leisure activities (domains included in SF-36 and Eq-5D). Proposed change (if any): Add non-health related QoL.	See above.
Section 3.4.2.2 (pg.95)	Clinigma	Comment: Another approach for using preference data side-by-side with clinical data is the use of a standard interview manual (SIM) developed by Clinigma. The SIM includes specific modules eliciting patient preferences and benefit-risk assessment as well as modules on diseases burden and patient impacts pre, during and at-exit of clinical trials.	See above.

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Section 4.2.2.3 (pg.110)	Clinigma	Comment on second bullet point: Which is often the case when developing new investigational drugs. What is often missing is the understanding of the value and importance that patients put to the drug benefits - why it can be very useful to interview trial patients about their assessment of the benefits or risks to ensure a correct description seen from the user's perspective.	See above.
Section 5.2 (pg.145)	Clinigma	Comment: Clinigma strongly recommends to involving patients participating in clinical trials in patient preference studies, as this will overcome many of the practical issues with recruiting patients with the relevant profile and countries of interest. The Retuxan Hycaela case showed that a preference study conducted in relation to a clinical trial can lead to successful outcome and even a labelling claim with the FDA.	See above.
Section 5.2.1 (pg.145)	Clinigma	Comment: It is a challenge if patients are not very familiar with all the benefits and risks of the treatments in focus. This is also why Clinigma recommends to recruit the patients from the clinical trials - as they have an experience with the drug in question. The Retuxan Hycaela	See above.

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
		case showed that a preference study conducted in relation to a clinical trial can lead to successful outcome and even a labelling claim with the FDA.	
Section 5.3.1 (pg. 146)	Clinigma	Comment: What is overlooked is the description of the benefits and risks. It can be very hard to describe at early stage of the drug development, as the data is based on safety-trials, and only at very late stage of the drug development the effects/benefits can be described better based on phase 3a/3b trials. Still there is nowhere the understanding of in what way the patients see the benefits and risks as meaningful or not. By interviewing trial patients about their experiences with the investigational drug, it is possible to gather early insights on how the patients experience the benefits and risks of the new drug, and if they see them as meaningful or not. This type of feedback can help with an earlier clarification of if the description of the benefits and risks are correctly described - thereby ensuring that the preference study has a correct and valid description of the new drug.	See above.
Section 6 (pg.151)	Clinigma	Comment:	See above.

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
		It looks like 3 bullets should be presented - only 2 are depicted.	
COMMENTS BELOW ON QUALIFICATION OPINION			
Lines 19-23	Clinigma	Comment: The PREFER website states that '*PREFER looks at how and when it is best to perform and include patient preferences in decision making during the medical product life cycle. We include patient stakeholders at every level of the project'* (Start - PREFER (imi-prefer.eu). Proposed change (if any): Consider adding 4th objective of PREFER '*To give patients a voice in drug development based on their expert experience'*	Agreed in principle, no change deemed necessary however; idea of patient preference studies is ingrained in concept/name.
Line 159 *Considerations of cognitive burden and capacity* pg. 72 of draft guidance	Clinigma	Comment: Population heterogeneity is an important issue. Disease-related aspects (such as time since onset, severity, etc.) as well as disease-unrelated aspects (such as attitudes, cognitive abilities, education & knowledge and/or experience with expected AEs, etc.) warrant consideration in study planning as well 161 as interpretation of results. Throughout the design process, a consideration on the cognitive burden and/or capacity of the participant should be kept at the forefront (pg.72)	Acknowledged, however no change necessary. Opinion text does not imply exclusion, but explains that this aspect warrants consideration for planning and interpretation" of PPS. This is deemed a valid and inclusive statement.

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		Proposed change (if any): To avoid at all times using cognitive capacity as a condition for patient participation in preference studies.	
Line 163-164	Clinigma	Comment: Furthermore, the participants' ability to think about and express preferences will often only be triggered by the explicit confrontation with choice options. Preferences can be elicited through open-ended questions without patients being confronted with choice options or use of methods such as swing weighting (SW).	Agreed. No changes made. Opinion text addresses this aspect in a cautionary way.
Lines 146-148	Clinigma	Comment: a systematic approach to selecting an appropriate method is not limited to the presented and discussed methods, and the provided list should not be considered prescriptive. Agree: patient experience data on meaningful change, burden of disease, impact on quality of life, and risk acceptability is key and can be elicited in ways other than listed.	Agreed; no change suggested.
General comments	IQVIA	• The current PREFER framework provides a detailed guidance on how to conduct patient preference studies using different quantitative methods based on the study objectives • IQVIA agrees with the Agency that the framework is useful in informing researchers on the process and what to consider when	Overall, the comments are acknowledged and partly agreed; however, no action taken, mainly based on scope of procedure. It is noted (and reflected as such in the Opinion) that the methods listed are non-exhaustive. Qualitative methods are not excluded. The topic of reflecting PPS data in submissions/output is also addressed adequately.

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
		conducting a patient preference study, how to select which quantitative method is most appropriate for estimating preferences (discrete choice experiment (DCE), best-worst scaling (BWS) type 1 & 2, swing weighting, threshold technique), what to consider when choosing the sample size, experimental design and analysis • The qualification opinion from the Agency notes that the examples described in the PREFER framework should be evaluated based on the study objectives and the robustness of the data, and there are different examples provided in the framework on how patient preference data can be used for medical product decision-making. Other possible preference methods are notably missing from the selection of available methods to elicit preferences (conjoint analysis, standard gamble, time trade-off, visual analogue scale, analytical process) and details when and how these methods can be used for medical product decision-making and in which context. These methods, along with other elicitation methods such as DCE, threshold technique, BWS type 1 & 2, and swing weighting, have previously been identified in the literature as promising elicitation preference methods likely to meet decision-makers' needs during different stages in the medical product lifecycle (Whichello et al, 2020). While IQVIA appreciates that the PREFER framework prioritised five key patient preference methods as a starting point, it is still important noting these additional methods	Lack of participants' experience with queried concepts is addressed (hypothetical/experienced vignettes). It is reiterated that this Opinion (and supplementary documentation) is not regulatory guidance. Seeking Scientific Advice for specific Questions is stipulated in the Opinion as is the possibility of reflecting PPS in regulatory documents. With regard to the subsequent comments on the IMI 'Framework' document please note that the 'Framework' document as such is not to be amended. Upon review, no changes to the 'Opinion' were deemed necessary based on the comments provided.

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
		used to collect preference data in the framework, given the specific research question. • In addition, there is minimal description in the PREFER framework on the relevance / applicability of solely using qualitative methods (focus groups, in-depth interviews, semi-structured interviews), to capture patient preferences. There would also be benefit in understanding which qualitative methods are preferred in the context of patient preference studies. For instance, do we expect focus groups to alter the elicitation of attributes or preferences of these attributes? These qualitative methods can be used not only to improve the accuracy and relevancy of proposed attributes and associated levels identified from the literature to take forward for the quantitative phase of the study, but also to explore what attributes are important to patients, why patients value different attributes, what do these attributes mean to the patients, and how do patients describe these attributes, using different words and phrases. • Another topic that is not explored is the use of qualitative patient preference data as an addition to an evidence dossier in the context of an industry submission package or in labelling documents. This would help understand whether qualitative data is also an option that can be included as key patient preference evidence to inform decision-making throughout the medical product lifecycle. IQVIA	

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		encourages the Agency to comment on the importance of qualitative research and how this is used to evaluate patient preferences. • Currently there are no references on whether experience with the treatment of interest is of importance. In the context of HTA reimbursements, often patients are asked to reflect on vignettes or provide hypothetical estimates of preferences without experiencing the treatment of interest. The applicability of these methods in a regulatory decision-making process is not addressed. • IQVIA also encourages the Agency to consider the differences between preferences informed by experiences (e.g., stated preferences following participation in a cross-over trial; revealed preferences in a long-term extension study) and those which are hypothetical in nature. This may be valued similarly but will be applied differently. For instance, the former is generally more appropriate for evidence supporting drug labelling SmPC, although both may inform approval and appearance in the EPAR. Currently the qualification opinion does not discuss the inclusion of patient preference data in labelling documents despite the discussion in the PREFER framework (section 3.4.3.3). The framework also provides an example study (Table 3-9 and 3-23) where data was derived in combination from a clinical trial sample (patients who have experience with the treatment) and a general population sample (those with no experience with the treatment).	

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		IQVIA would like the Agency to provide guidance on which approach is most desirable, and whether these samples may be complimentary or viewed differently, particularly for a label claim. • IQVIA agrees with the Agency that the inclusion of patient preference data may depend on a case-by-case basis given the research question, however this may also be due to the limited number of submissions with patient preference data to be used as a guidance. While the current PREFER framework provides various examples and suggestions for use of patient preference data for regulatory submissions, some regulators and other stakeholders may require additional familiarity and interpretation of patient preference data to provide guidance and recommendation for regulatory use. One suggestion is to develop and include in the PREFER framework a graphic decision tree or model to give guidance on the different preference methods to be used for various research questions in different contexts. • More broadly, IQVIA encourages the Agency to define whether early questions about patient preference research should be a target for each scientific advice with the Scientific Advice Working Party or whether there is another preferred mechanism by which the Agency can offer guidance to pharmaceutical groups.	

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Figure 1 – Qualification Opinion	IQVIA	Comment: The PREFER framework should also include a dissemination component in Phase 3. There are concerns that patient preference studies are often classified as market research activities with dissemination often not actively encouraged, leading to a potential publication bias in the medical and scientific literature. Proposed change (if any):	Framework document not to be amended. Partly agreed; The possibility to reflect PPS in regulatory documents has been addressed in the Opinion text. Uptake in PP register is recommended; propagating (academic) dissemination deemed beyond scope. No action taken.
Figure 1-1- PREFER Framework	IQVIA	Comment: The current PREFER framework highlights that patient preferences and PROs are entirely distinct; however, the text then uses the Rituxan Hycela study as an example of a patient preference study (Table 2-1). Preferences in this trial were elicited using questionnaires asking about patients' treatment experiences and outcomes (PROs) to conclude that Rituxan Hycela is preferred. In addition, some key questions proposed by PREFER are proposed to be answered using patient preferences (e.g., benefit-risk trade-offs); however, some PROs can also be used to address these questions. IQVIA welcomes the Agency to provide their insights on patient preferences vs PROs. Proposed change (if any):	Framework document not to be amended. Partly agreed, beyond scope of Opinion;
Section 2.4.3.2 – PREFER Framework	IQVIA	Comment: IQVIA encourages the Agency to express a need for assessing the content validity of patient preferences – by demonstrating that attributes / associated-levels are relevant but also that the task is not	Framework document not to be amended. Opinion lines 169-182 address this topic on adequate level. No action taken.

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		too cognitively burdensome for the target population to complete. Currently the PREFER framework discusses the validity and reliability of patient preferences in section 2.4.3.2; however, IQVIA recommends the Agency commenting on the importance of the cognitive complexity of the task and the interpretability of the data. Proposed change (if any):	
Section 4 – PREFER Framework	IQVIA	Comment: In section 4 of the PREFER framework, some quantitative methods include specific examples and graphics in the text for individuals to better understand the method at large, while descriptions for other methods (swing weighting, BWS type 1 & 2) only provide details on why the method would be used and key references for further information. It is important for stakeholders and regulators to become familiar with the different patient preference methods to better understand which is most suitable for different stages in the medical product lifecycle, so providing clear examples with graphics of all discussed methods will allow the audience to understand what the preference data will look like and how it can be easily interpreted. IQVIA encourages the Agency to suggest a clear example for each different patient preference task (e.g., how it's presented to patients), what the results look like and why this task is important to stakeholders and regulators (the 'so what') under the methods section.	Framework document not to be amended. Providing examples for each method beyond scope of opinion. No action taken.

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
		The applicability of patient preference methods, which method in an in-person or electronic format is also of relevance, given how certain preference methods are difficult to translate electronically. Proposed change (if any):	
General comments	EFPIA	EFPIA welcomes the support for preference studies as expressed by the positive tone of the EMA draft qualification opinion. This should help support the use of preference studies as a robust tool for collection of patients' views, and thus is consistent with the EMA's (and industry's) objective of working towards more incorporation of patients' views into medical product decision-making. In particular, reference is made to EMA regulatory strategy 2025 objective of <<include patient preferences to inform the benefit-risk assessment>> The multi-stakeholder collaborative approach in PREFER has been instrumental in the development of a framework which will increase patients' representativeness in drug	Acknowledged, no action taken;

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
		development and in decision making by prescribers, regulators and HTA bodies. EFPIA particularly welcomes EMA's approach ensuring that PPS information is included in key regulatory documents such as the EPAR. This helps strengthen the acceptability of PPS information from a broader range of stakeholders including HTAs and Payers. Further specific comments on this section are provided below. It is recognised that this document is a Qualification Opinion and not a Guideline. In the specific comments, some suggestions and requests/suggestions are made which may therefore be considered out of scope for the purposes of this Qualification Opinion. However, EFPIA would like nonetheless to highlight these topics so that they be considered for future guideline development, which will help ensure full and consistent implementation of the principles outlined in this Opinion.	
65 - 79	EFPIA	<u>Comment:</u> In this paragraph the EMA discusses previous efforts to incorporate quantitative and semi-	No action taken. Use/reliance on PPS data in the context of regulatory decision making will be decided on a case-by-case basis, as elaborated in the Opinion.

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		quantitative methods to weight efficacy and safety data for benefit-risk assessments. Do these quantitative methods refer to the use of patient preferences in benefit-risk assessments? Can the EMA please clarify their position on the use of patient preferences for regulatory benefit-risk assessments?	
77 – 79	EFPIA	Comment: We welcome the EMA emphasis on patient preference studies as a tool which can promote a more structured inclusion of patients' views in the regulatory decision-making process.	Acknowledged.
80 - 88	EFPIA	Comment: This paragraph about the potential decision scenarios in which patient preference data could add value is especially helpful, and congruent with the content in lines 461-468 of the draft FDA benefit-risk guideline.	Acknowledged.
106 - 107	EFPIA	Comment: We welcome the statement that the framework can serve as a structure for regulatory-industry interactions, and the overall support for the framework.	Acknowledged.
109 - 114	EFPIA	Comment: We would suggest adjusted language about the 'soft' nature of preference-sensitive decisions.	Partly agreed; paragraph revised, incorporating some of the suggested text.

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		Proposed change: Introducing the concept of 'preference sensitive situations' (section 2.1 in the briefing documentation) was questioned with regards to its added value and necessity during interaction with the applicant. **The concept of 'preference sensitive situation' is intended as a high-level summary of the situations described in lines 80-88, specifically the potentially concerned (decision) scenarios.** ~~It is found of limited value in assisting in the identification of relevant contexts of use in the regulatory setting. The conditions/categories listed to describe PP-sensitive situations appear rather soft and any eventual judgment of whether they would apply in a certain situation would remain subjective (as well as dependent on the experimental design).~~	
115 - 116	EFPIA	Proposed change: ~~This~~ **The latter** was accepted by the Applicant during the Discussion Meeting and a reference in this respect is added to the qualification opinion.	Acknowledged; sentence changed to read: ~~This was accepted by the Applicant during the Discussion Meeting and~~ A reference in this respect is added to the qualification opinion.
118	EFPIA	Comment: The registry being referred to is the "Health Preference Study and Technology Registry",	Agreed, corrected name and added link.

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		suggest EMA to include the hyperlink as well for easier reference. https://hpstr.org/landing	
122 - 123	EFPIA	Proposed change: **The framework may furthermore support interactions between industry, regulators (and HTA bodies/payers, as well as patients).** Overall, it is agreed that the framework is suitable for informing on objectives, design and conduct, and reporting of PPS.	Not agreed. Already stated in lines 106-108.
135 - 136	EFPIA	Proposed change: These methods (described in chapter 4 of the ~~framework~~ **briefing book**) differ with regard to the experimental setup, the design space as well […]	Partly agreed; removed bracket.
155 – 157	EFPIA	Comment: Please clarify the term "targeted elicitation" does this refer to the target population or a well phrased survey question. Does "estimation task" refer to estimating a preference weight?	The 'targeted elicitation' refers to the overall elicitation exercise. Addition to statement made in text.
158 - 168	EFPIA	Comment: Disease severity is a very important patient characteristic, but it is not always easy to obtain. It might not be in the medical record and patients might not be reliable in self-reporting it. Time since onset is often used, but	Acknowledged, but beyond scope. No action taken.

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
		maybe it is time to recommend ways to extrapolate it. The EMA comment on attributes that a patient never experienced or is unfamiliar is a critical concern. It might be partially remedied by having low vs. high severity subgroups, but not always. For example, for a drug treating 5 menopausal symptoms, women might only have 2-3 symptoms out of 5 and not all women might experience the same 2-3 symptoms over time. Further detail and guidance on how to characterise these attributes would be welcome.	
158	EFPIA	Comment: Health literacy is the patient capacity understand and use healthcare information and is different to the broader term "education & knowledge". Comment: Also take into account possible physical disabilities from participants, which may influence the use of devices and access to clinical trials and therefore the results. Proposed change: Population heterogeneity is an important issue. Disease-related aspects (such as time since onset, severity, etc.) as well as disease-unrelated aspects (such as attitudes, cognitive	Accepted, text added as suggested;

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
		abilities, education & knowledge, **health literacy, physical disabilities** and/or experience with expected AEs, etc.) warrant consideration in study planning as well as interpretation of results.	
180	EFPIA	Comment: the potential negative impact on subject is a common ethical question occurring in any clinical trial, not only in PPS. Proposed change: In addition, as with any clinical study, participating in a PPS may have the potential to negatively affect subjects depending on information presented and appropriate care/measures should be in place to mitigate respective concerns.	Agreed in principle, no changes needed; wording as is considered cautious enough ("may have potential").
187 - 188	EFPIA	Comment: There are a few possible interpretations of (cross)validation for example using two different preference approaches to measure preferences in the same sample, or qualitative piloting of the preference instrument prior to the main data collection. These have different implications on the feasibility of the study depending on the target disease, for example in rare diseases it may be more challenging to validate given the smaller patient population.	No action taken; both interpretations are valid (i.e. sequence of explore/confirm; use different preference methods)

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		Can the EMA clarify what is meant by (cross-)validation efforts in this sentence and discuss the implications for therapeutic areas with smaller patient populations?	
205 – 206	EFPIA	Proposed change: For these aspects, the PtC offers limited information at present, **but is a field of rapid growth.**	No change deemed necessary.
210 - 212	EFPIA	Comment: We welcome the EMA approval of the chapter on points to consider for method selection (and acknowledge the caveats expressed about selection of preference methods).	Acknowledged.
216 - 222	EFPIA	Comment: We appreciate the EMA's agreement to including preference data in the Clinical Overview, as well as in the EPAR or other relevant documents. An insight in to how the PPS or any Patient Evidence was used in the overall benefit risk evaluation will be invaluable to prescribers, industry and downstream stakeholders and rewarding to the patients who provide their time and resource. However even when a submitted PPS was not considered in the context of a regulatory decision, it would be useful to provide a rationale (in the appropriate document e.g. EPAR) as to why this was not considered relevant and what criteria were	Acknowledged. Not considering a PPS (based on assessment or relevance) for decision making may be reflected in assessment documentation (e.g., in EPAR).

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
		applied by reviewers to assess utility (e.g. Population used was not representative of the patient population). Such transparency will provide an opportunity to develop the science and share best practices.	
220 - 222	EFPIA	Comment: This statement requires clarification: "More generally, the value of conveying information on group-level preferences to individual patients in relevant documents would have to be carefully considered for situations where individual choice is paramount (i.e., for prescription or administration/use)". Almost all data in an SmPC is based on comparison of groups. Robust preference study results could contribute to individual choice even if it reflects group level preferences. Clarity on what is meant by 'relevant documents' and more defined criteria for inclusion in each should be developed as experience is gained.	The analogy is not agreed to. No change necessary.
219	EFPIA	Proposed change: The decision will be made on a case-by-case basis, **taking into account the validity and robustness of the data**	Partly agreed; yet no action taken as other considerations (e.g., perceived relevance) may also play a role.
228 - 229	EFPIA	Comment: The framework is endorsed but there is no specific advice nor recommendation to consider it for any new PPS planning.	Acknowledged, no action taken. Wording adequate as is.

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
		Proposed change: The proposed research framework and points to consider document is generally endorsed as a comprehensive reference document for planning and conducting patient preference studies (PPS). **Given the absence of existing framework, we advise to consider this framework for planning and conduct of a patient preference study. [...]**	
230 - 231	EFPIA	Proposed change: However, specific comments are made and several potential limitations are addressed above, ~~specifically also with regard to identification of preference sensitive situations.~~	Not agreed; no action taken.
254-255	EFPIA	Comment: The draft opinion makes a brief statement that 'scientific advice at the planning stage is encouraged'. From a sponsor perspective, a more detailed description of the Agency's expectations and process for seeking advice on patient preference methodologies in particular would be helpful.	Acknowledged, yet outside scope. No action taken.
General Comments	JDRF	JDRF is pleased that the EMA has generally endorsed the IMI PREFER framework but recommends the agency consider developing formal guidance.	Acknowledged, no action taken.

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
General Comments	JDRF	The collection and utilization of patient preference data is important for the advancement of T1D therapies.	Acknowledged, no action taken.
General Comments	EuropaBio	We generally support the implementation of frameworks like that which is being proposed by IMI-PREFER and appreciate comments and input provided by the European Medicines Agency (EMA). While the IMI-PREFER framework is a potentially appropriate approach to generating robust patient preference information, we concur that there are a number of other patient preference study approaches that can be used. Flexibility should be routinely applied to determine the most appropriate methods that should be used based on research objectives, target population, and regulatory goals. Patient perspectives on preferences for treatment attributes and benefit-risk considerations are important to consider when evaluating the overall benefit-risk of a treatment. If available, patient preferences should be routinely considered to help inform EMA's interpretation of the overall benefits and risks of a treatment in a target patient population. Patient preference information is	Acknowledged, no action taken.

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
		becoming an increasingly important component that can be valuable to support regulatory decision-making, with added value in rare conditions and novel therapeutic contexts where uncertainties remain. Reinforcing patient relevance in evidence generation was one of the top three core recommendations across all stakeholders during the EMA consultation on its Regulatory Science Strategy (RSS). We believe that EMA should aim to develop broad and flexible guidance on patient experience data generation (including that of patient preference information, if appropriate) to help fulfil RSS goals. Likewise, we believe that efforts should be made to harmonize these recommendations with international stakeholders (i.e., FDA, ICH) to facilitate and guide the generation, use and submission of patient experience data to support regulatory submissions and benefit-risk considerations. As industry partners, we look forward to working with EMA to put these recommendations into effect in the context of a multi-stakeholder discussion.	