9 April 2021
EMA/194133/2021

Overview of comments received on 'ICH reflection paper on proposed ICH guideline work to advance patient focused drug development' (EMA/CHMP/ICH/415588/2020)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	EATG, David Haerry
2	EATG, Bryan TEIXEIRA
3	Galapagos NV
4	Merete Schmiegelow, Patient advocate
5	Centre for Patient Reported Outcomes Research at the University of Birmingham
6	European Hematology Association (EHA)
7	Medicines for Europe
8	GSK
9	EFPIA
10	Vesa Kataja, MD, Chief Medical Officer; Mari Metso-Lintula, MD, Medical Director; Laura Lang, MMSc & MSc, Healthcare data scientist for Kaiku Health Ltd, Helsinki, Finland
11	Gilead Sciences Inc.
12	European Federation of Statisticians in the Pharmaceutical Industry (EFSPI) / Statisticians in the Pharmaceutical Industry (PSI)
13	UCB Biopharma SRL
14	EORTC
15	Eurordis
16	European Forum for Primary Care (EFPC)
17	Thalassaemia International Federation

Please note that comments will be sent to the ICH for consideration in the context of the ICH process.

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1. General comments – overview

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1	0	Better define the term "patient" / "patients" and use the terminology developed with EMA input through EUPATI-IMI, published Published: https://doi.org/10.3389/fmed.2018.00230	Defining "patient" The term "patient" is often used as a general, imprecise term that does not reflect the different types of input and experience required from patients, patient advocates and patient organisations in different collaborative processes. In order to clarify terminology for potential roles of patient interaction presented in this and the other EUPATI guidance documents, we use the term "patient" which covers the following definitions: "Individual Patients" are persons with personal experience of living with a disease. They may or may not have technical knowledge in R&D or regulatory processes, but their main role is to contribute with their subjective disease and treatment experience. "Carers" are persons supporting individual patients such as family members as well as paid or volunteer helpers. "Patient Advocates" are persons who have the insight and experience in supporting a larger population of patients living with a specific disease. They may or may not be affiliated with an organisation. "Patient Organisation Representatives" are persons who are mandated to represent and express the collective views of a patient organisation on a specific issue or disease area. "Patient Experts", in addition to disease-specific expertise, have the technical knowledge in R&D and/or regulatory affairs through training or experience, for example EUPATI Fellows who have been trained by EUPATI on the full spectrum of medicines R&D.

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			There may be reservations about involving individual patients in collaborative activities with stakeholders on grounds that their input will be subjective and open to criticism. However, EUPATI, in line with regulatory authorities, instils the value of equity by not excluding the involvement of individuals. It should be left to the discretion of the organisation/s initiating the interaction to choose the most adequate patient representation in terms of which type of patient for which activity (see section 7). Where an individual patient will be engaged it is suggested that the relevant patient organisation, where one exists, be informed and/or consulted to provide support and/or advice. The type of input and mandate of the involved person should be agreed in any collaborative process prior to engagement.
2	0	A significant amount of patient input (the majority?) may be qualitative data. It may be helpful to have more clarity about what kinds of qualitative data, with what criteria of robustness, trustworthiness, etc., are preferable in general and specifically/especially within clinical trials...but this may be for a later step in this process.	
3		It is appreciated that the ICH reflection paper clearly recognises the importance of global alignment and that future guidance intends to make optimal use of existing initiatives.	
4		Overall: A high appreciation for ICH taken the initiative to acknowledge the importance of having patients perspectives integrated in medicines discovery and	

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		development as well as part of the regulatory decision making,. i.e. from early on through out the entire process until approval covering the entire ICH members as well as those countries/regions taking the ICH recommendations into account. This is a very important global step further for both patients, sponsors and regulatory authorities to increase the quality, relevance, benefit/risk and information to the decision-makers. The draft, reflection paper covers in a structured manner a broad examples of opportunities for integrating patient perspectives during the entire medicines Research & development (R&D) and approval processes, although not exhaustive as indicated in line 71. The opportunitie are huge, although focus are agreed to the need for two new ICH guidelines covering what (COAs) and how (methods), respectively, are agreed to as global, standards/harmonized manners to identifying, collecting and analysing meaningful, prioritised patient perspectives. It is important that two key points are taken into account: 1. The standars should not be so complex and time consuming that it delay or even prevent the significant timewise and economic benefits of having patient perspectives as a natural and important part of medicines R&D and decision-making 2. The involved patients keep a true declaration of "no conflict of interest" in relation to the concerned	

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		pharmaceutical industry. Update of the ICH M4E (CTD), ICH M8 (eCTD) and E6(R3) (GCP) are also important to take the integration of patient perspectives into account. Please ensure patients are involved in those future related ICH updates and/or developments. For the below, specific comments Nos. 3-6 are very important to take into account from a patient advocate perspective. Comment No. 2 is categorised as minor,, while the above general, comment No. 1 is categorised as very important, too.	
5	B	Guidelines issued by ICH should be applicable to all disease areas, not just specific to a particular medicine discipline (e.g. oncology – the EMA Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man – https://www.ema.europa.eu/en/documents/other/appendix-2-guideline-evaluation-anticancer-medicinal-products-man_en.pdf). Patient-Reported Outcomes Tools: Engaging Users & Stakeholders PROTEUS (https://www.pcori.org/research-results/2018/proteus-patient-reported-outcomes-tools-engaging-users-stakeholders)	
		The following references around PRO and tolerability should be included to strengthen the guidelines (Broadening the Definition of Tolerability in Cancer	

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		Clinical Trials to Better Measure the Patient Experience – https://www.focr.org/sites/default/files/Comparative%20Tolerability%20Whitepaper_FINAL.pdf) PRO alerts and electronic PRO use: Patient-Reported Outcome Alerts. Ethical and Logistical Considerations in Clinical Trials – https://jamanetwork.com/journals/jama/article-abstract/1741830 Management of Patient-Reported Outcome (PRO) Alerts in Clinical Trials: A Cross Sectional Survey. – https://doi.org/10.1371/journal.pone.0144658	
		Currently, CPROR is working on the development of a guidance on the ethical considerations for the use of PROs in research and routine practice. The guidance is being developed according to the Guidelines for Reporting Health Research by the EQUATOR Network. Our recommendations might be a helpful point of reference when developing ICH guidelines in this area. An announcement piece has been accepted for publication in Nature Medicine. Cruz Rivera S., Mercieca-Bebber R., Aiyegbusi L. O., et al. "The need for ethical guidance for the use of Patient-Reported Outcomes (PROs) in research and clinical practice", Nature Medicine, 2021 (in press).	
6		The reflection paper is very well written, structured and covers the key-issues to prepare the implementation of an important, novel instrument in drug development. The topic is complex and so will be the process. As mentioned in the reflection paper, it is crucial that this endeavour is	

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		done in collaboration with all the stakeholders. The patients/families' rights and integrity must be ensured. It could be helpful to focus on a limited number of (existing or new) methods to translate patient preference into drug development for the sake of harmonization and standardization. It could be considered incorporating simplified binary futility questions, mirrored between patient and treating physician, such as: "has this treatment been useful for me/my patient" to gather better insight into basic correlation/discordance between perspectives.	
8		Overall, the content and intent of the reflection paper is welcome and important. We agree with the proposed future topics for ICH guideline development; however, other potential topics should be considered. For example: guidelines that address patient perspectives on unmet needs, input into trial design, protocol development and supporting better enrolment and retention. If guidelines are developed, it may be helpful to include sections on how patient perspective information will be used and what weight will be attached to it versus traditional physician-determined endpoints. Also, it would be helpful to understand the extent to which early patient qualitative data would influence early scientific meetings and the expectations around collecting such data.	

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		Another area of interest is clinical trial-embedded interviews, which are increasingly used to understand the patient experience, in addition to COAs. The ICH guidelines could consider the utility of such trial-embedded qualitative research and how such data might be used by regulators. In the context of vaccines development, patient-reported outcome (PRO) measures are also important. There are some specificities associated with the application of PROs in the context of vaccine development, which should be considered. To have a deeper understanding of the background of using PROs in vaccine development programmes, we reference and provide a link (https://www.tandfonline.com/doi/full/10.1080/21645515.2021.1875762) to the following publication: Curran D, Sabater E and Nelsen L. .2021 "Patient Reported Outcomes in Vaccines: Relevance for Decision Making" *Human Vaccines & Immunotherapeutics*, Volume 17 Issue 9.	
		The paper mentions that guidances should start after substantial completion of existing guidances such as the FDA PFDD guidance and IMI Prefer work. It would be helpful to also discuss specific areas of alignment and any areas that may expand upon current work. To the extent that guidances can be harmonised globally would be helpful in terms of implementation.	Discuss how ICH guidances may align, harmonise, or build upon existing guidances.

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9		EFPIA appreciate and support ICH's commitment to advancing a Reflection Paper that identifies key areas of incorporation of the patient perspective to improve the quality, relevance, safety and efficacy of drug development and inform regulatory decision-making in a globally harmonized approach that is methodologically sound, sustainable for the regulated industry and regulatory authorities, and spans the full lifecycle of drug development. Moreover EFPIA support the ICH Reflection Paper's proposed plan to enable broader stakeholder participation by applying lessons learned and best practices from the ICH E6(R3) public consultation so that stakeholders beyond ICH participants can contribute. We also support the ICH proposal to progress the development of a harmonized acceptable approach for how to assess applicability of results across regions and/or cultures, similar to how the ICH E5 Ethnic Factors in the Acceptability of Foreign Clinical Data addressed extrinsic factors (e.g., cultural and environmental). Finally, we are encouraged to see that ICH plans to leverage existing regulatory guidances, a number of ongoing collaborative efforts, and a large body of existing literature that would support the efficient development of these proposed PFDD guidelines.	
		EFPIA have the following general issues: • **Patients' involvement:** Patients' insights should be collected throughout the drug development process, however the Reflection Paper focuses primarily on clinical	

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		trials. • **The role of the caregivers:** Their role on the wellbeing and understanding of the impact of a treatment on the patient (particularly if the patient is not in a condition to communicate that information) is often underestimated. Could their voice also be considered in such documents? • **Diversity and inclusion:** EFPIA believe it is of major importance to explicitly address diversity and inclusion in the patient engagement process and noticed the passive reference to the subgroups in the Reflection Paper (RP. The RP does not discuss the issues of patient needs at the level of different communities. Instead, we notice the RP seems to state that all patients, when taken together, have the same levels of access and the same overarching needs and constraints. Of course, we acknowledge that this is maybe more of an issue in the United States than elsewhere, so we acknowledge that addressing this concept in an ICH guideline might be challenging. • **Reference to existing guidance documents and initiatives:** The RP mentions that there are a range of services, sources etc... in the patient involvement space, with reference to the FDA guidance and IMI PREFER; however it would be useful to also include reference to the co-created IMI PARADIGM Toolbox, which provides recommendations, tools and relevant background information to make patient engagement in medicines development easier for all. This tool box (https://imi-paradigm.eu/petoolbox/) covers planning patient	

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		engagement, conducting patient engagement and reporting & evaluation. Similarly, there is a lack of references to ongoing or completed guidance documents (e.g., the FDA PFDD Guidance I, published in June 2020).	
10	1	With great pleasure we at Kaiku Health Ltd acknowledge the EMA/CHMP/ICH initiative to renew the international GCP guidelines. Especially we want to praise the aim to advance patient focus in drug development. The traditional very much (surrogate) efficacy parameter based clinical trials have focused to disease outcomes, in cancer care, to the cancerous disease burden and/or to the tumor. The patient has been a rather passive provider of information on eg. Adverse events and quality of life data, if asked. Thus, the best provider for data on the real effectiveness of the treatment has been in shadows. What matters most to the patients and to the society is the real value of the treatment; both in humane and economical terms. Many new and very expensive drugs enter the market and clinical use with rather limited efficacy results based on surrigate markers only, which as such, may not fulfill the expectations and values of the patients. The statements here by the representatives of Kaiku Health Ltd concern mainly cancer treatments and patients suffering from cancer.	
		About Kaiku Health and what we have done in this field.	

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		Kaiku is a digital health intervention platform (DHI) created to improve cancer patients´safety during their cancer treatments and follow up after treatments. Kaiku collects electronic patient reported outcomes (ePRO) from cancer patients and provides data direct to patients´ health care professionals (HCPs). With Kaiku, ePROs are monitored in an active manner instead of the traditional passive PRO data collection done in clinical trials. Collected data, patients´ symptoms arising from cancer treatment, helps clinicians and investigators to early detection of serious adverse events and disease progression. Having ePROs a part of cancer care has been shown to increase patients´ time on treatment, decrease the severity of adverse effects (severe adverse events, SAE), emergency room (ER) visits and hospitalization and also increase overall survival (OS) (1-3). Kaiku´s symptom questionnaires are treatment-based questionnaires and have been used in clinical trials, drug development and in routine care in many European countries. Patients are able to fill the questionnaires via electronic applications like smartphone, tablet or computer and report symptoms through the assigned questionnaires to the clinics. Kaiku Health has collaborated with several pharma companies for better understanding of patients' experience in treatment and drug development in phase II – III trials. Our own experience has been that the collaboration with pharma companies is very productive and benefiting the patients.	

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		Pharma companies have found ePROs as useful tools to have in their drug development. Collecting patient reported symptoms in cancer care there is possibility to create models for predictive symptom management by using machine learning and artificial intelligence. With predictive capabilities in the DHI applications patient safety, treatment tolerance and co-operation will be much improved and getting more realistic end points in trials, and also more comprehensive data about drugs under development, becomes feasible. We have published several abstracts of Kaiku´s feasibility in general use as an ePRO and also in symptom prediction with our collaborators in cancer care, ie. Patients, hospitals and pharma industry. References: 1. Basch E et al. Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. JAMA. 2017;318(2):197. 2. Denis F et al. Two-Year Survival Comparing Web-Based Symptom Monitoring vs Routine Surveillance Following Treatment for Lung Cancer. JAMA. 2019;321(3):306–307. 3. Basch E, Deal A, Kris M, Scher H, Hudis C, Sabbatini P et al. Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A	

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		Randomized Controlled Trial. Journal of Clinical Oncology. 2016;34(6):557-565. 4. Schmalz O, Jacob C, Ammann J, Liss B, Iivanainen S, Kammermann M, Koivunen J, Klein A, Popescu RA. Digital Monitoring and Management of Patients With Advanced or Metastatic Non-Small Cell Lung Cancer Treated With Cancer Immunotherapy and Its Impact on Quality of Clinical Care: Interview and Survey Study Among Health Care Professionals and Patients. J Med Internet Res. 2020 Dec 21;22(12):e18655. Doi: 10.2196/18655. 5. Iivanainen S, Ekström J, Virtanen H, Lang L, Kataja V: Predicting objective response rate (ORR) in immune checkpoint inhibitor (ICI) therapies with machine learning (ML) by combining clinical and patient-reported data. Ann Oncol (2020) 31 (suppl_7): S1428-S1440. 10.1016/annonc/annonc391 6. Popescu RA, Ekström J, Leemann H, Virtanen H, Kataja V: Predicting patient-reported symptoms for patients undergoing immune checkpoint inhibitor (ICI) therapies using different measurement system than in prediction model training. Abstract accepted and presented in the Swiss Oncology & Hematology Congress as ePoster, 18-21 Nov 2020. SOHC (2020) 7. Iivanainen S, Alanko T, Vihinen P, Konkola T, Ekstrom J, Virtanen H, Koivunen J: Follow-up of Cancer Patients Receiving Immune Checkpoint Inhibitor Therapy by Electronic Patient Reported Outcomes-tool (KISS): a pilot feasibility study. JFR (2020) 4: (10):e17898. Doi: 10.2196/17898	

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		Iivanainen S, Ekström J, Virtanen H, Kataja V, Koivunen J: Predicting the onset of immune-related adverse events (irAEs) in immune checkpoint inhibitor (ICI) therapies using a machine learning (ML) model trained with electronic patient-reported outcomes (ePROs) and lab measurements. Ann Oncol (2020) 31 (suppl_4): S1057, https://doi.org/10.1016/j.annonc.2020.08.1488 8. Iivanainen S, Ekström J, Virtanen H, Kataja V, Koivunen J: A combination model of electronic patient-reported outcomes (ePROs) and lab measurements in prediction of immune related adverse events (irAEs) and treatment response of immune checkpoint inhibitor (ICI) therapies. Ann Oncol (2020) 31 (suppl_4): S1068. https://doi.org/10.1016/j.annonc.2020.08.1523 9. Iivanainen S, Ekström J, Kataja VV, Virtanen H, Koivunen J: Electronic patient-reported outcomes (ePROs) and machine learning (ML) in predicting the presence and onset of immune-related adverse events (irAEs) of immune checkpoint inhibitor (ICI) therapies. J Clin Oncol (2020) 38 (suppl_15): e14058-e14058. Doi: 10.1200/JCO.2020.38.15_suppl.e14058 10. Iivanainen S, Ekström J, Virtanen H, Koivunen JP: Predicting onset and continuity of patient-reported symptoms in cancer patients undergoing immune checkpoint inhibitor (ICI) therapies using machine learning. Annals of Oncology (2019) 30 (suppl_11): xi16-xi32. Doi: 10.1093/annonc/mdz449.004	

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		11. Iivanainen S, Alanko T, Peltola K, Konkola T4 Ekström J, Virtanen H, Koivunen JP: ePROs in the follow-up of cancer patients treated with immune checkpoint inhibitors: a retrospective study. J Cancer Res Clin Oncol (2019) 145: 765. Doi: 10.1007/s00432-018-02835-6	
11		We would welcome a structured process to incorporate the patient preference data into regulatory submission to inform regulatory decision making. Currently the FDA Regulatory Submission Checklist for patient experience data from both clinical trials and non-clinical trials is not a clear roadmap as to what is expected and needed for a 16avourable submission. We would welcome more clarity to provide more transparency. How will the data be scored and 'coded' to have utility for programmes in the future? Is there a consideration of transferability of results from one disease state to another? (Eg if disease state 1 had 'pain' or 'sleep disturbance' as key criteria to be addressed would these data be transferrable to disease state 2?) Standardisation would achieve some consistency of patient experience as they interact with pharma, but how do competitive interests play out in this context? i.e. what level of standardisation is aspired towards?	

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		What is the scope for differentiation in how a pharma company interacts with patients? What are some of the questions that development organizations can start proactively answering as they go through regulatory approval?	
12		It may be worth to add (e.g. in appendix) the definition of patient's perspective and patient preference, so that the text can be better understood. Definition of patient preference (CDER, 2016) is provided in the table (page 3) but it does not clearly appear as a definition.	
13		We welcome the opportunity to submit comments on the ICH reflection paper to advance patient-focused drug development. Comments on proposed Guidance on COAs: We endorse the proposal of not restricting guideline scope to patient-reported outcome instruments, in favour of a guideline covering all types of clinical outcome assessments (COAs). We strongly value the reference to 'concepts' (line 44), as it is time to move away from an 'instrument-led' approach to a 'concept-led' approach to best capture what matters most to patients. Likewise, we strongly support the reference to 'qualitative and quantitative methods', since mixed method research is best suited to generate holistic and patient-centred evidence. Qualitative methods are of particular relevance in rare	

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		diseases and in paediatric, elderly and cognitively impaired populations. Supporting the proposal that the guideline covers methods around the definition and interpretation of clinically meaningful within-patient score changes, we believe that emerging novel methodologies should be acknowledged as valuable complements to the legacy anchor-based and distribution-based methods, such as qualitative methods (see J Patient Rep Outcomes 2019 Mar 4;3(1):16 for example). We suggest including in the finalised guideline clear references to modern test theory approaches, which add value in generating genuine patient-centric measurement *(see references as examples).* *Comments on proposed Guidance on Patient Preferences:* We appreciate the inclusion of guidance on the methods and approaches that can be used to measure the benefit-risk trade-offs from the patient perspective. Beyond benefit-risk trade-offs, patient preference information can also be used to provide valuable patient-centred insights along the drug development pathway. Therefore, we strongly propose the guidance document present a clear position on the situations where patient preference information can add value to regulatory decision making. Further, we would value specific guidance on when patient preference data, that is collected outside clinical	

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		trials, would be acceptable by regulators. In our experience, patient preference data collected outside of a clinical trial can be combined with clinical data to provide valuable insights into patients' treatment preferences that can inform the interpretation of clinical data (e.g., benefit-risk trade off). *General comments that apply to both guidance documents:* Industry would welcome more clarity on the following aspects in the finalised guidelines: • "Robustness" criteria for regulatory and payer decision making. • "Overview of quality standards" to help understand and differentiate study quality (and raise overall evidence generation standards). • Definition of "Patient Experience Data (PED)" to help align diverse perspectives (e.g. creating a Global Taxonomy). While it is anticipated that COAs and patient preferences will be explored in two separate guidance documents, COAs and patient preferences are complementary, and both provide valuable information about the patient experience. We suggest that this position is reflected in the guidance documents and recommendations on an approach how both can be used in a complementary manner is explored. Further, it would be valuable to	

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		acknowledge that while COAs and patient preferences allow for the collection of patient experience data, PED themselves cover a broader field. As stated in the document, line 87-89, "not everything identified as important by patients, caregivers and clinicians is measurable" and the question, line 57, "what disease effects and treatment burdens matter most to patients" is a critical one to be answered including with qualitative data. We also believe that the future guidance should adopt a more holistic perspective and incorporate patient experience to inform not only regulatory decision making but also value assessment decision-making processes (i.e. Health Technology Assessment). Convergence with the HTA approach to patient experience data, by involving HTA representatives in guideline development, should be sought. We also support the proposal to revise ICH M4E and ICH M8 to harmonize regulatory requirements for reporting and submission of patient experience data to regulatory authorities. We recognise your work on reflecting other outputs (e.g. FDA) to optimise synergies while drafting this guideline to ensure development of genuine international guidance to advance patient focused drug development.	

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		We hope our comments will be helpful in improving this reflection paper and are looking forward to the finalised document.	
14		The EORTC would like to congratulate the ICH for their initiative in providing guidance on how to best include the patient's perspective into the drug development program. We would also like to thank the ICH for the opportunity to review this document. We have reviewed the ICH reflection paper at the EORTC, both from a clinical trial perspective (i.e., the added value of including the patient perspective in EORTC cancer clinical trials) and a measurement perspective (development of patient-reported outcome measures in oncology). We believe putting patient at the center of drug development is essential. Capturing patient preferences is critical and will need to be done using robust methodology generating useful information. Capturing patient preferences will be important to design sound and relevant clinical trials. Investigating patient experience via the collection and analyse of patient reported outcomes during clinical study is a must. Analysing the true impact of a health intervention via meaningful clinical outcome assessments is critical. Nevertheless, it will be important to clarify what will be the new requirements for clinical study sponsors and researchers. It has to be kept in mind that new obligations should aim	

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		to improve the quality and relevance of drug development but without jeopardizing the conduct of clinical research because of unrealistic expectations We would also like to be included in the development of these guidelines as this topic is of interest to us, both as a PRO instrument developer and an academic clinical trial group. Please find our comments and suggestions below: 1. The guideline stresses the need for standardized methodology for identifying, collecting, and analysing that what is meaningful to patients. However it should be stressed that where appropriate standards already exists (eg. Validated questionnaires, core outcomes, standardized reporting, …) that in these instances the groundwork does not need to be repeated for each new study. More specifically, we would like to highlight following the initiatives and guidelines: • Development and validation of PROs, including elicitation of relevant outcomes o EORTC module development guidelines (https://qol.eortc.org/manuals/) o COSMIN (cosmin.nl) • Translations and translatability of PRO instruments	

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		o EORTC module development guidelines (https://qol.eortc.org/manuals/) o ISPOR (Wild D, Grove A, Martin M, et al. Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health. 2005;8(2):94-104) • Identifying core outcomes o COMET initiative (https://www.comet-initiative.org/) • PRO analysis o SISAQOL/SISAQOL-IMI (https://event.eortc.org/sisaqol/) • PRO reporting o CONSORT-PRO (https://www.equator-network.org/reporting-guidelines/consort-pro/) o SPIRIT-PRO (https://www.equator-network.org/reporting-guidelines/spirit-pro/) • PRO interpretation including meaningful change o ISOQOL psychometrics group and mixed methods group o SISAQOL/SISAQOL-IMI (https://event.eortc.org/sisaqol/)	

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		o PRO-MID (https://promid.mcmaster.ca/) Of special note, the PROTEUS initiative aims to promote systematic use of methodologic tools developed to optimize the design, analysis, reporting, and interpretation of PROs in clinical trials. (https://more.bham.ac.uk/proteus/) 2. We appreciate the inclusion of these core assumptions in the document. We agree that measures that will be used to assess the patient perspective should be developed with the idea that this will be used to assess the same disease in multiple regions of the world. Ensuring that these measures are developed simultaneously in multiple countries (guaranteeing translatability) should be considered best practice. The EORTC has standardized guidelines on how to develop PRO measures for various cancer diseases that takes into account the patient perspective from various countries and cultures. This can be used as a reference in the development of such measures for other diseases. 3. Additional questions that are relevant in the discovery and development phase should include a. What is the patient reported experience regarding their disease and treatment? How can this information be incorporated in the benefit/risk assessment in clinical trials?	

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		b. How does the disease and treatment impact a patient's health-related quality of life? Which aspects of HRQOL are impacted by these therapies? c. Are there specific symptoms or concepts for which patient reporting is especially key? E.g., issues that may be less reliably measured by clinician reporting and biological indicators alone? 4. When discussing clinical meaning change, there are two issues to be distinguished: a. What change within in a patient can be considered as meaningful. This is a property mainly of the selected endpoint itself and relates to the concept of Minimal Important Differences in PROs. b. What magnitude treatment effect would be considered worthwhile. One cannot expect all patients to benefit equally from an intervention. Trials must be designed to detect a pre-specified treatment difference. However the magnitude of such treatment difference must be sufficiently substantial to justify the risk-benefit of the treatment on a population level. 5. The guideline should address that the controlled clinical trial environment is not necessarily representative of the real world. Therefore issues obtained from real world data may not always transfer to the clinical trial setting and vice-versa. In addition, constraints of specific clinical trial designs may impact on the elicitation,	

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		collection, analysis, reporting and application of patient-oriented outcomes. As an example, a randomized clinical trial may be blinded to treatment allocation by addition of a placebo drug. This impacts the patients' perception by adding uncertainty to his/her treatment status and discomfort by requiring to comply to a medication schedule.	
16		Our EFPC working group is enthusiast. This is a very relevant step in making pharmaceutical care more adequate and relevant for patients. The paper is for political reasons formulated in an only positive approach. Yet, we would like to hear the problems that make this switch to a clear patient centered approach necessary. It is well known that patient information on many drugs are downplaying the side effects of drugs (e.g. contraceptives, but also A II inhibitors, LUTS-drugs, etc.) Many drugs also are hardly clinically relevant (e.g. psychopharmaceutics, chemotherapy). The intrinsic problem of the for profit orientation of the industry is often at odds with objective, independent presentation of facts, patient information and even research. If we could agree in this paper on the problem analysis, that would be ideal. But we can see that such an approach would divide and kill this project in its start. Yet it would be in the patients interest, when the research would be totally independent with no ownership by Pharma. It would also be helpful if the information on drugs as well as the text	

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		of the prescription would be independent of the owner of the drug. (e.g. owned by the EMA) Key question: are there specific primary care related viewpoints on patient-focused drug development? The reflection paper starts with what seems a new paradigm – the patient's perspective -. An immediate reaction could be early approval of medications and vaccines before completion of their clinical trials on clinical complications. But "patients' perspective is also the relevance of safety and efficacy". It is also difficult for primary care to communicate news of treatment when there is no consensus and potentially growing uncertainty, with fear of potential new disruptions to come. Since the Covid pandemic started we have learned more about the disease and diagnosis regarding treatment, similarly to when HIV started and within a decade became a treatable condition and patients are safely managed as any other chronic diseases. Patients group were part of developing treatment. Covid19 also brings its new cultural stigma, - elderly and isolation - . The progress in understanding the disease came with its set of constraints. The EU has got an existing system that provide feedback, the current dilemma is: it must be timely and in full details but on the other hand provided as quick as possible. Patients' cultural needs, and specific understanding of symptoms or value are part of primary care work, which is sometimes helped with sociology ethnology or	

Stakeholder no.	Section No.	Comment and rationale	Proposed change / recommendation
		psychological and ground field experience. How is EMA going to capture what is known from this social science field? Good clinical evaluation of trials and follow up of released medication, increasing use of this new pharmaco-epidemiology discipline, using and developing local scientific knowledge and networking with European projects is needed. For example, it would be good if the industry acknowledge that Hep C and Covid19 research and patients need are not that different but price of treatment clearly differ. The other argument is that primary care team members are also patients, or their family and they also have this experience. One might question a treatment that saves life – cancer treatment – and due to side effects – peripheral neuropathy – impair one convalescence and survival life. A good example was developed previously with the Diabetes UK study, started with a database on diabetes and gradually evolving into research and knowledge. It would be interesting to start a similar approach with patients complaining about fatigue as this is such a common presentation in primary care. The other lesson from Diabetes UK is that science evolves and for instance in Ischemic Heart Condition beta blockers were once life savers according to Cochrane –	

Stakeholder no.	Section No.	Comment and rationale	Proposed change / recommendation
		now the question is if they are or do they need to be taken only for one year to be life saver? The European project -Druid – on road accidents and prescription of drugs provided knowledge and data which were not acted upon as possibly too political sensitive. From a primary care perspective we also need to include community pharmacists and other Primary Care professionals who are not mentioned in the guideline. In a time of remote access – and increasing use of delivery services even for medicine – taking away from another local first line contact – possibly a source to capture patients' symptoms. Currently in the UK they work with clinical pharmacists, primary care Centre employing pharmacist (non-dispensing).	

2. Specific comments on text

Stakeholder no.	*Line no.*	Section no.	Comment and rationale	Proposed changes / recommendation
13	5-61		Whilst we appreciate the proposed ICH guideline stems from and is aimed at regulatory authorities, we believe that the future guidance should adopt a more holistic perspective and also aim to meet the evidence requirements from other healthcare decision-makers, such as Health Technology Assessment bodies. The latter, too, are increasingly endorsing the value of patient perspective into their own decision-making processes. Any divergence across healthcare decision-makers on the definition of acceptable, reliable, valid and representative patient experience data may result in conflicting decision-making outputs, which may ultimately negatively impact timely access for patients to novel therapies.	"inform regulatory, **and health technology assessment (HTA)** decision making" (lines 5 and 61)
7	6-8		Patient satisfaction with new processes put in place for patient-focused drug development is essential. This should be reflected in the wording of the guideline.	We would propose to amend the sentence as follows: It also presents opportunities for development of new ICH guidelines to provide a globally harmonized approach to inclusion of the patients' perspective in a way that is satisfactory for the patients as well as methodologically sound and sustainable for both regulated industry and regulatory authorities
6	9-50	A	General comments on section A: Most early development programs in cancer, including hematological cancer, take place in incurable cancers with highly limited treatment options; they	

			evaluate therapies aiming to prolong patient life and it seems likely that, in this setting, any demonstrable effect on life prolongation will trump other factors such as patient experience. However, the transition from early phase, in which drugs may be used at maximum dose in order to not jeopardize efficacy signals, to later phase clinical research in non-end-of-life settings often does not take the changing scenario into account and leads to frequent licensing of drugs and their combinations at doses and posologies that are not optimal for patient experience. Both this and post-approval research with the aim of label changes seem to be areas where patients' perspectives should be much more strongly incorporated. Very significant progress for patient wellbeing has been made in post-approval academic clinical research; e.g., demonstration of lower toxicity of low-dose dexamethasone or significantly reduced rate of peripheral neuropathy with subcutaneous and weekly bortezomib in multiple myeloma. This research was partly patient-driven and has likely spared thousands of patients unnecessary side effects. However, as it was never a regulatory requirement and/or submitted to regulators, these improved ways of drug delivery have not found their way into drug regulatory labels. Still to date, this allows for new research to be conducted using sub-par comparator arms based on clinically outdated regulatory labels to patients' detriment. Tolerability and patient preference research should be made mandatory post-approval by regulators. Frameworks should be developed in particular for flagging drugs that showed disproportionate risk/benefit scores in patient evaluation in early stages of development, and for committing stakeholders to post-licensing research that should feed directly into the license label again if improved ways of administering drugs are identified. This could be enforced via a new conditional approval mechanism that takes patient experience gathered in early research into account, whilst acknowledging that early drug development is particularly complex and often has to focus on efficacy, above all.	

9	10		Patients have direct experience however, it is recommended to include "caregivers", especially for mentally impaired patients as caregiver's perspective is crucial.	Patients **and caregivers** have direct experience in living with a disease.
6	10-11	A	"Patients have direct experience in living with a disease": the wording suggests that this pertains only to chronic diseases.	Patients have direct experience in living with a disease (chronic or temporary).
5	10-14	A	It would be beneficial to provide additional information about rationale for greater use of patients' perspective throughout the drug development process. Following references could strengthen the message: EPIC study – Systematic Evaluation of Patient-Reported Outcome Protocol Content and Reporting in Cancer Trials – https://academic.oup.com/jnci/article/111/11/1170/5430934 Patients experience – Defining Patient Experience – https://pxjournal.org/journal/vol1/iss1/3/ Research waste and outcomes to patients that matters – Maximising the impact of patient reported outcome assessment for patients and society – https://www.bmj.com/content/364/bmj.k5267 FDA Patient-Focused Drug Development Guidance Series – https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical PROs in RWE development – Harnessing the patient voice in real-world evidence: the essential role of patient-reported outcomes – https://www.nature.com/articles/d41573-019-00088-7 PROs in the regulatory decision-making process – Incorporating the patient experience into regulatory decision making in the USA, Europe, and Canada – https://www.sciencedirect.com/science/article/pii/S1470204518300974?via%3Dihub	

15	10-14	A	The key word here is **"Perspective**." It is not essential to have "Lived experience" of a disease in order to have a patient perspective, although of course it certainly helps. But just as important is an ability to consider all of the implications of any given action, outcome measure or other objective in terms of its likely consequence for patient welfare and outcomes. The "Naive" patient will rarely have this kind of insight and is often far too easily influenced by others to express the viewpoint they are seeking, even if neither side recognises this is happening.	Patients have direct experience in living with a disease, **and their representatives have professional skills to use this experience for R&D and evaluation purposes**. They have firsthand knowledge of the impact of the disease on their life and on how they feel and function. They bring a unique and valuable perspective to drug development, one that cannot be provided by the clinical, scientific, legal and other experts. It is important for health authorities and for drug developers to incorporate the patient's perspective, beginning early in drug development.
			A missing key word is **Commitment**: Patients and their representatives tend to be fully committed to the search for safe and effective treatments, as they have "skin in the game". Researchers are certainly conscientious in their approach to the task, it is however of a different order to that of someone who is committed.	Patients have direct experience in living with a disease, and their representatives have professional skills to use this experience for R&D and evaluation purposes. They have firsthand knowledge of the impact of the disease on their life and on how they feel and function. They bring a unique and valuable perspective to drug development, one that cannot be provided by the clinical, scientific, legal and other experts. It is important for health authorities and for drug developers to incorporate the patient's perspective, beginning early in drug development.
9	13-14		'It is important for health authorities and for drug developers to incorporate the patient's perspective, beginning early in drug development'	It is important for health authorities and for drug developers to incorporate the ~~patient's~~

			Comment: As patients' perspectives are considered in drug development, it is essential to qualify that the impact is on average. Lines 13-14 refer to a patient's perspective i.e., the individual patient, rather than to patients' perspectives. This background section sets up an unrealistic expectation that drug development will evolve to a unique, singular patient. The text throughout the document should be made clear that any input from patients (plural) would be implemented in a clinical trial or in a drug development program, on average. That as we identify what exactly can be measured, there will be a mean and a standard deviation that will influence rather than a separate solution for individual patient preferences.	**patients'** perspective, beginning early in drug development
10	13-14	1	Patient reported outcomes (PROs) have been collected in clinical trials and also in routine clinical practice for decades; thus we are not dealing with a new thing. They have been collected eg. With different questionnaires first in paper format, later as electronic. Quality of life questionnaires have also been there earlier. In a way the patient's perspective has been there to some extent.	
9	14		Patient's perspective might be considered even earlier during research phase/pre-clinical studies	It is important for health authorities and for drug developers to incorporate the patient's perspective, **at research or in** ~~beginning~~ early development phase
10	18-19	1	One of the major problems with the earlier approach has been the vast heterogeneity of the ways of collecting PROs and including QoL data.	
10	20-21	1	See above. In addition to identifying, collecting, and analysing what is meaningful to patients, also the utilization of the data has not been optimal, or not at all there.	
15	20-24	A	Maybe to add a definition on patient centricity, patient focused research? ISPOR published this one, with the contribution of patients: "The active, meaningful, and collaborative interaction between patients and	In many instances patient focus is already considered in traditional development plans, and patient input, when needed, is already

			researchers across all stages of the research process, where research decision making is guided by patients' contributions as partners, recognizing their specific experiences, values, and expertise." Rachel L. Harrington, Maya L. Hanna, Elisabeth M. Oehrlein, Rob Camp, Russell Wheeler, Clarissa Cooblall, Theresa Tesoro, Amie M. Scott, Rainald von Gizycki, Francis Nguyen, Asha Hareendran, Donald L. Patrick, Eleanor M. Perfetto, Defining Patient Engagement in Research: Results of a Systematic Review and Analysis: Report of the ISPOR Patient-Centered Special Interest Group, Value in Health, Volume 23, Issue 6, 2020, Pages 677-688, ISSN 1098-3015, https://doi.org/10.1016/j.jval.2020.01.019.	sought except that the methods for identifying, collecting, and analysing what is meaningful to patients, are not standard or harmonised. Similarly, systematic studies of patient preferences may not be necessary in many clear-cut situations but when they are, it would be beneficial that the methods follow agreed standards. On possible definition of patient focused research could be "The active, meaningful, and collaborative interaction between patients and researchers across all stages of the research process, where research decision making is guided by patients' contributions as partners, recognizing their specific experiences, values, and expertise."
17	20-24	A	We agree with this approach. Nonetheless, there is an omission regarding the actual integration of the patients' views into development plans.	We suggest to add that: "**Even if the patients' comments and suggestions are sought and collected, their integration into development plans remains voluntary. Therefore, there is no mechanism to assess whether the patients' views have been indeed taken into account for the improvement or finalisation of such plans**".
6	22-23	A	The sentence "...studies of patient preferences may not be necessary in many clear-cut situations…"	It could be helpful to add an example to contextualize the sentence
13	23-24		It would be beneficial to provide explanations for and examples of "clear-cut situations" and "study quality".	

15	23-24	A		it would be beneficial that the methods follow agreed standards **and are informed by patient input at the design stage.**
9	25		Scope for data collection tools for high quality source of evidence should be both within and outside of clinical trials.	If methodologically-sound data collection tools are developed and used within ~~clinical trials~~ and sound standards for the analysis for the analysis, reporting and application of the results are developed and used…
8	25-28		The COVID pandemic has demonstrated the robustness of different approaches to study conduct that are more patient-friendly, including remote monitoring and direct shipment of oral study drug. This is expected to improve the patient's clinical trial experience and could result in increased participant compliance and diversity. Virtual / telemedicine approaches, e-consenting, home visits for assessments and sample collection, etc are also a part of these evolving approaches.	It would be good to see ICH guidance on novel approaches to study conduct. The guidance should also include a section on ways to obtain patient input on the value of such novel approaches. Add a paragraph providing guidance on how study conduct can be more patient friendly.
10	25-28	1	Methodologically sound, safe and easy-to-use collection tools already exist. These tools are not only passive collectors of data, but at best they provide predictive capababilities for further enhancing patient safety. See description of Kaiku Health platform at the end.	
13	25-28		It is unclear whether this paragraph is referring to just patient preference studies or whether it is referring to both patient preference studies and COAs. It is important to note that patient preference studies can be used to inform all stages of drug development and therefore not necessarily conducted within a clinical trial.	
5	30-37	A	Currently, CPROR is conducting work on the usage of PROs in the real-world setting, by addressing priorities set out in the article: "Harnessing the patient voice in real-world evidence: the essential role of patient-reported outcomes" – https://www.nature.com/articles/d41573-019-00088-7	

			Evidence generated within a routine care environment can be of paramount importance to inform long-term effectiveness & safety of medicinal products. The ICH guideline should also cover recommendations for use of PROs generated in the real-world setting.	
10	30-37	1	It has already been shown that including ePROs into clincial practice will enhance patient's adherence to treatment, increase safety of the treatment, enables modifications to the treatment so that the treatment may be "tailored" to the patient, which in turn allows picking out early those most probably not benefiting from the treatment and, on the other hand, allowing longer treatment continuum for those who are potiential benefitors. Digital monitoring of PROs is an effective strategy to continuously engage and assure the health of patients and it should become a cornerstone for population health management in oncology.	
4	34	6	"recruitment and" should be added after support and before adherence to ensure equal focus on those factors and in line with enrollment (line 35)m and retention (line 36).	Support "*recruitment and" adherence*
9	36-37		Designing trials that support better enrolment and retention – it is suggested to revise the text as proposed since patients' input would presumably be also of value to pricing and reimbursement agencies.	Designing trials that support better enrollment and retention, **and decrease the burden on patients and caregivers**; informing regulatory decision making including patient acceptability of benefits vs risks vs tolerability concerns, and effective risk management.
15	36-37	A	The same paragraph proposes to collect the views of patients for the delopment of products about "product design features including formulation and delivery modes that minimize burden and support adherence", however for their role in informing the decision-making, acceptability of benefits vs risks vs tolerability concerns, and effective risk management are mentioned. To be consistent, it could be important to add the possibility to inform on the	informing regulatory decision making including patient acceptability of benefits vs risks vs tolerability concerns, effective risk management, **and also patient concerns**

			ease of use, compliance issues, and/or product design in the regulatory decision making as well.	**on product design, adherence issues, and on ease of use.**
8	37		Patient quality of life is not explicitly mentioned (perhaps it is implied). This is an important factor not only in clinical trial design but also in decision-making, e.g. risk-benefit determination.	State the importance of patient quality of life more explicitly
16	38-39		unnecessarily vague. Employ methods & measures. Is EMA and EC starting independent research. Are they demanding independent patient oriented research from the pharmaceutical industry.	Please be explicit on what research should be replaced by this new patient oriented research.
10	38-46	1	There is a discrepancy in what is regarded as "symptom" reported by the patient and what is constituted as an adverse event/adverse drug reaction related to treatment in real life. It has been shown in several trials that physicians and other HCP tend to underestimate the frequency and the severity of the symptoms suffered by the patients (Di Maio M, Basch E et al. Patient-reported outcomes in the evaluation of toxicity of anticancer treatments. Nature Reviews 13: 319-325, 2016). The patient records in clinical practice are not a reliable source for data on the toxicity of the treatment. The picture one gets from there is not a real one. Epro data has been profiled as real world data of quality of life (QoL). The usage of ePROs has usually been placed in RCT phase III or phase IV in drug development. For better understanding of drug safety and for more practical patient selection to the trials there is an unmet need for collecting patient reported symptoms as early as phase II trials. It is important to collect patients´ experienced symptoms, not only patients´ QoL or Aes reported by HCPs, to get the whole picture of safety and tolerance of the drugs in cancer care. To achieve best results for patient safety the monitoring should be done interactively, not passively collecting ePROs as it is normally done in the clinical trials. Interactive monitoring decreases the potential risk of the study participants by enabling real time patients´ safety information at the time of the study. It could also shorten the timelines of the trials, both pre- and	

			post-marketing trials, and drug withdrawals as patients´ voice is heard in early phases of trials. To add actively collected patient reported symptoms to the trials from phase I, would complete ICH´s proposed reliable data generation by a new strategy and action for effectively and efficiently supporting quality in studies.	
2	40	9	Reliability and validity are well-established terms in quantitative analysis, but not as clear in qualitative analysis. Since the paper is open to qualitative analysis, it might be best to use more generic terms when talking about research in general, e.g., trustworthiness, rigour, bias-free.	See previous column.
8	40		add a line regarding the fact that regulators and drug sponsors should ensure that documents they use, and the outcome of the research should be made available for patients, caregivers and the broader community in a language which they can easily understand. Feasibility of collection should also be addressed.	Add: "All information should be made available for patients in a language which they can easily understand". The feasibility/practicalities of collecting patient perspective data should also be considered.
17	40-41	A	An additional point needs to be added further below, as the collection of reliable data implies that expert patients are identified and involved in such consultation processes, in collaboration with patient associations (if any) and/or treating physicians.	We suggest to add the following: "**ensure the information collected derives from expert patients, i.e. people who know in-depth the pathophysiology, clinical expression, complications and multi-disciplinary management of their disease and are familiar with drug development processes, policies and other such documents that affect the health and quality of life of patients at the national, regional and international levels**".
8	43-45		In the context of cancer – for example – and for other conditions, it may go beyond 'same disease' to stages of a disease – i.e. patient perspectives of	Include a line acknowledging potential differences of patient perspective that may relate to disease stage or severity

			early stage of disease may differ from late stage. This is alluded to at line 105 but could be made more explicit here.	
6	44	A	The sentence "…reflect concepts (e.g., pain, fatigue, physical function, etc.) that matter…" can be modified to emphasize that the patient's perspective addresses both effect and safety issues	"…reflect concepts (e.g., pain, fatigue, physical function, adverse events, etc.) that matter…"
7	40-46	A	Collection of patient information should occur in a way that is transparent and understood by patients	We would recommend to add one point to the bullet points list after line 46: - ensure that the information, including Patient-Reported Outcomes, is collected and processed in a manner that is transparent and clearly communicated to patients
11	41	A	There is a need to clarify "planning" and "decision-making" Does "planning" refer to the development of the product and the related planned clinical studies ? While "decision making" would refer to regulatory for Regulators, does "decision making" include that of sponsors' with regards to a drug development program ?	
11	46	A	Does heterogeneity include stage of disease ?	
16	47-50		This suggests a completely parallel research line (methods and measures), parallel to what is happening already regularly. That is in fact a waste of means and personnel. The proposed research should be replacing – possibly invalid - research proposed and initiated by the industry to prove the effectiveness of the drug, to finetune the promotion and marketing.	Pinpoint where the new research is going to make a difference.
8	51-63		In vaccine development, PROs could support the assessment of symptom severity in breakthrough cases after vaccination and also help to develop case definitions in case of symptoms based definitions.	Inclusions of two additional questions:

				What are the key symptoms reported by the patients that could be used in the case definition of patients? Is the burden of disease less severe in those who develop breakthrough disease after vaccination?
11	51-73		Which groups of patients / advocates do they suggest approaching to get the best insights in the most efficient way?	
12	55-63	B	We understood that the list of questions is not an exhaustive list. However, it could be beneficial to add a question link to enrollment, adherence or retention of patients in Clinical studies. Indeed, Patient's perspective can also support the design of clinical studies to improve the enrollment, adherence, and retention of patients in the trial (as mentioned line 36) and the current questions don't reflect this opportunity.	
15	55-63	B	One important contribution patients and their representatives can have is on the conduct of the research, i.e. the acceptability of the clinical trials constraints, areangements and provisions which repsect ethical considerations etc.	To add: - **How can the trial design and practical arrangements be improved to ensure high patient retention?**
9	56		What are the patients' unmet needs? – suggest deleting "potential drug targets", this should be about understanding patient experience of the disease in its entirety rather than whether there's an aspect of the disease that's druggable.	What are patients' unmet needs ~~that suggest potential drug targets?~~
15	56	B	New drug targets are important for unmet medical needs, and also for situations where the medical need is met but for a certain time. For example drug resistance can occur, or immune evasion. The drug effect vanishes after several months or years of satisfying response to treatment. Of course it depends on the definityion of an unmet need, which could encompass this situation. However, most often unmet need is used for conditions where no	What are patients' unmet needs that suggest potential drug targets? Or needs that are only partially or temporarily covered?

			treatment exist at all, or only symptomatic ones and not disease-modifying ones. Or there is some benefit, but partial only.	
16	56		*What are patients' unmet needs that suggest potential drug targets?* • Remedies for Non-medical condition – wellbeing - Vitamin's minerals and over the counter supplements, diets, cold remedies for adults and for children, vaccinations side effects in particular flue or Eustachian Tube dysfunction, nondependent sleeping aids, overweight, abdominal painkillers (Irritable bowel disease, periods delayed or periods pains in particular adolescents, hormonal replacement therapy), muscles and painkillers (Fibromyalgia osteoarthritis), mental health (depressed mood, memory changes). • Occupational diseases. Neurodegenerative diseases – Parkinson, Alzheimer and peripheral neuropathy - Fertility treatment, lungs disease – antenatal conditions, infectious pediatric (postnatal<one year old, < 8years old) in suburbs areas and elderly – immunization, urinary incontinence and protection pads, Pediatric mental – depression - health endocrine perturbation.	
7	56-63	B	Methodological considerations on patient experience data collection, processing and storage should also be included in the drug development process	We would recommend to add one point to the bullet points list after line 63: - What modalities of patient experience data collection, storage and processing are acceptable?
9	57-58		Proposal to add "addressed by a medical therapy and/or intervention", as it could be that the patient believes a device + therapy would be the best combination, so clarifying whether this is just limited to therapies administered on their own or in combo with other interventions may be useful clarity	What disease effects and treatment burdens matter most to patients that might be addressed by a medical therapy **and/or intervention?** (How) does this vary by subpopulation?

16	57-58		*What disease effects and treatment burdens matter most to patients that might be addressed by a medical therapy? (How) does this vary by subpopulation?* • Cold symptoms, persistent coughs, abdominal and periods pains including endometriosis, multiple cardiovascular drug regimen – diabetes and ischemic heart disease - and trying to simplify the prescription. Mental health Hypertension and diabetes, hairs related product, respiratory asthma in Afro Caribbean culture Infectious disease including hepatitis, Mental Health in Asian culture. Wellbeing and disease prevention supplement including food supplement. Recreational drug use, including CBD, antispasmodic and muscles relaxant, prescribing in pregnancy and postnatal, prescribing in elderly.	
8	59		see comment on lines 25-28	Expand bullet "What would be the best way to measure these effects and how acceptable are these to the patient?" to include
11	59	B	Even though this list is not meant to be exhaustive, the treatment burdens from a patient perpective is an important element to assess as part of an acceptable therapy.	Suggestion to add "assess the treatment burdens"
16	59		*What would be the best way to measure these effects?* • Cost effectiveness technology • Patient satisfaction, Quality of life Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011; 20:1727-1736. • Develop further and support existing tests developers – following episode of Covid19 -.	

11	60-61	B	Not only should the endpoint be robust enough to inform regulatory decision making but also suitable to be included in the labelling to inform patients.	
12	60-61	B	To avoid that the 'endpoint' prematurely is drawn into the discussion and that the 'patient perspective' is lost, consider rewording the 4th bullet to "What impacts and concepts are most relevant to patients and what endpoints can be constructed to capture these concepts? Can these endpoints be incorporated in clinical trials in a manner that will be robust enough for regulatory decision making?"	
16	60-61		*What endpoint are most relevant to patients, and can these endpoints be incorporated in clinical trials in a manner that will be robust enough for regulatory decision making?* • Primary care and Hospital attendances, Quality of life including existing tools and regional reporting system	
9	62		What is a clinically meaningful change in an endpoint from a patient perspective? – it is suggested deleting "clinically"	What is a ~~clinically~~ meaningful change in an endpoint from a patient perspective?
16	62		*What is a clinically meaningful change in an endpoint from a patient perspective?* • Number to treat and Outcome measures- absolute risk reduction. • Transparency with pharmaceutical industry conflict of interest. • Stock availability.	
10	62-63	1	Traditional clincial trials in cancer care use mostly surrogate markers for evaluating the treatment effect. Many of these are not at all relevant to the patient, especially when advanced/metastatic disease is the target. For example progression free survival (PFS) with varying definitions from trial to another, is totally irrelevant for the patient unless it is associated with relief of symptoms. It should not be used as a surrogate for overall survival; in that it has not been proven a valid measure, except for a few occasions. A	

			meaningful change in a patient over time is best defined by the patient him/herself.	
9	63		How to define meaningful change in a patient over time? – suggest changing "in" to "for"	How to define meaningful change ~~in~~ **for** a patient over time?
4	63-64	9	Extra bullet to be added to ensure the right measurements can create any evidence based data supporting any patient perspectivemtext in the Product Information. Even it is mentioned that the indicated questions are not exhaustive, the topic is significant important to think in from early on to be able to get an authority approved, qualitative patient perspective statement in he final Product Information. If not indicated as a visible bullet, it is frequently postponed in the clinical development programme often causing too weak justification for authorities to accept a qualitative patient perspective statement in approved Product Information.	Additional bullet after line 63 and before line 64: "* *Consider from early on throughout the development process wording on patient perspectives in the* *Product Information (e.g. SmPC and PIL) supported by meaningful, clinical, relevant data"*
6	64	B	Questions regarding patient preference may also include "how patients should be informed"; e.g., by the Sponsor, a GP, a specialist, and is it done in writing (on the layman language) and/or in a conversation such as before accepting a clinical trial.	A bullet on "How patients should be informed" could be added
8	64		consider patient subgroups	Add a bullet point: "are there specific patient subgroups to consider?"
13	64		We acknowledge that on line 71, it is mentioned that this is not an exhaustive list. However, we recommend including at least one example in the list that demonstrates a use of patient preference data beyond benefit-risk trade-offs. An example of a possible additional bullet point is proposed below.	How can patient preference data be used beyond understanding benefit-risk trade-offs? (e.g., understanding the relative importance of other aspects of treatment

				such as process attributes and health-related quality of life)
16	64		*Questions related to patient preference—relevant throughout development—could include:* • What is the gain in quality of life? • What is the length and cost of treatment for patient?	
8	65-70		The acceptable trade-off is likely to vary depending on the nature and stage of the disease, particularly for progressive conditions.	acknowledge that patient perspectives on this point, e.g. tolerability/risk acceptance are likely to vary from patient to patient and how this could be addressed, i.e. how to avoid the 'one-size fits nobody' outcome that can arise when results/responses are averaged-off
10	65-70	1	In cancer care, there are two very distinct treatment entities, ie. treatment to cure and treatment to palliate. Much due to the current end points used in advanced/metastatic cancer (PFS, tumour shrinkage, number of metastases) the focus is in what happens to the disease/tumour, not what happens to the patient. The drugs that are able to shrink the tumour are rendered the best, no matter how much toxicity to the patient they may cause. "T‟e treatment was well tolerated" ”s a rather common conclusion in cancer drug trials where in fact 90 % of the patients suffer from adverse events, 30-40 % from serious adverse events, and some die due to treatment related complications. Considering the fact that the shrinkage of the tumour is a poor correlate to the patients overall prognosis, this kind of an approach needs to be changed. Especially if the patient dies due to treatment that is supposed to be palliative, the whole idea of the treatment as palliation has gone totally wrong.	

			A lot of clinical drug development occurs in the very late phase of the disease, ie. in the 3rd treatment line and beyond, and drugs approved in this setting are eventually also used. What is said about palliative treatment above, is especially true in this setting. Active drug treatment in the last months of a cancer patient's'life is rather common. According to some studies active treatment is given in 10 - –0 % of the cases during the last 30 days before death. This is not only due to clinical imcompetence. It also reflects the twisted expectations both the physicians and the patients have on the capabilities of cancer drugs. Treating false hopes of a patient with toxic substances is nothing but a disservice to everyone. Especially in this setting the patients' 'oice should be heard carefully.	
16	69-70		*What are methodological considerations for sponsor conduct of patient preference studies to provide credible and reliable findings to support regulatory decision making?* • Independent from pharmaceutical industry trial, no conflict of interest.	
11	70	B	Should this refer to "independent" findings as well?	
4	70-71	11	Extra bullet to be added to ensure the right methodologies used for measuring the right patient relevant factors can create any evidence based data supporting any patient perspective yext in the Product Information. Even it is mentioned that the indicated questions are not exhaustive, the topic is significant important to think in from early on to be able to get an authority approved, qualitative patient perspective statement in the final Product Information. If not indicated as a visible bullet, it is frequently postponed in the clinical development programme often causing too weak justification for authorities to accept a qualitative patient perspective statement in approved Product Information.	Additional bullet after line 70 and before line 71: *" * Consider from early on what authority accepted method(s) should be used and what are the minimum* *size of meaningful, patient relevant perspective data required to support a qualitative, patient staterment* *in the Product Information (e.g. SmPC and PIL)".*

10	74-80	1	There is an urgent need to actively include patients in the drug developing process from the very start of it, the latest in the phase where the patients are subjected to the drug. Although important, prolonging survival is not always the ultimate goal the patients see. The trial protocols already should include patients' views on the goals of the particular treatment, especially when the trade of for gaining something is the toxicity one must suffer.	
3	76-77	C	Galapagos NV welcomes the ICH's recent reflection paper on proposed ICH guideline work to advance patient focused drug development. We support the general approach in including valuable patient perspectives to inform drug development programs and related regulatory decision making. In addition to the topics outlined in the current reflection paper we would like to suggest that the topic of Bring Your Own Device technology (BYOD) is also considered in the new guideline. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) both support remote patient research and the use of electronic tools to collect patient data. Furthermore, recent research has demonstrated high level of patient acceptance towards using BYOD in clinical trials. However, a lack of clear guidance on the implementation of BYOD in clinical trials is making risk-averse sponsors hesitant in including this mode of data collection in their clinical trials. In our opinion, there is a growing need to address this issue and provide more comprehensive guidance on the use of BYOD for data capture in clinical trials.	We propose that the future ICH guidance, in addition to the proposed qualitative and quantitative methods and the COA types also addresses data capture tools and in particular BYOD use in clinical trials.
8	76-78	Table	Include vaccines development in Topic C	Include a question on vaccines development: can PROs be used in case definitions and/or to trigger identification of cases?
			Regarding discovery /development in general - It's relevant to consider condition, indication and type of therapy. Appropriate endpoints will vary by condition and by treatment, i.e. some treatments,	

			indications, populations do not lend themselves to typical efficacy or safety endpoints, or to randomized trials etc. Therefore, it's important that any guidelines are flexible in their application and aid the identification of appropriate (and helpful) patient-perspective measures.	
			In the context of preference-based methodologies, discreate choice experiments (DCEs) have been commonly used to (1) estimate difference in utilities between health states; and (2) help to prospectively identify which outcome of a trial is more relevant to the patient (Curran *et al* 2021.)	We would propose to focus on developing the recommendations on: • Criteria and Best practice to determine the optimal attributes and level within preference-based studies • Propose methodological recommendations to address the potential sources of bias in preference-based studies. Best practices for quantitative analyses of the outcomes from preference-based studies
16	76-78	Table (Box left on top)	*What disease effects and treatment burdens matter most to patients that might be addressed by a medical therapy? (How) does this vary by subpopulation?* • Cardiovascular effects • Risk for Infectious diseases • Cancerous effects • Mental health effects • Neurodegenerative effects *What would be the best way to measure these disease or treatment burdens/effects in a clinical trial?*	

			• Reduce impairment or resolve it, and time limited prescription. *What would be the most appropriate endpoints to use in clinical trials (and robust enough to inform regulatory decision making)?* • NNT (Number Needed to Treat), absolute risk reduction *What is a clinically meaningful changes in an endpoint from a patient perspective?* • Resolving or limiting the reason for prescription indication. • Stop taking the prescription. *How to define meaningful change in a patient over time?* • Return to basal status, with limited or no consequences.	
16	76-78	Table (Box right on top)	*Qualitative and quantitative methods to identify disease/treatment impacts important to patients that would be candidate concepts for measurement with patient reported outcome (PRO) measures or other types of COAs or in quantitative assessments of the patient perspective.* • The approach to organize and structure the content of the guideline document would undergo further consideration as this work advances under an ICH new topic proposal. One approach would be to develop the main document with an extensive focus on common considerations for all COAs and include annexes with considerations that may only apply to certain COA types such as observer reported (ObsRO), clinician reported (ClinRO), performance based (PerfO) measures, etc.	
6	76-80	C	Comments on table (page 2): It should be highlighted that much groundwork is required to identify patient opinion in the initial stage both for disease effects & treatment burdens as well as preferences. This should be done by impartial third parties (i.e.,	

			researchers). Patients should not just be 'involved' but become an expert source of equal standing to other stakeholders during this process. Methodologically, this process should be based (or at least include) a series of interviews, focus groups and Delphi processes, groupwork sessions with patients and physicians, etc. to identify issues or topics that should be addressed. Furthermore, to agree about the way in which these topics will be measured. Following this stage, questionnaires can be designed and presented to the participants for validation - respondent validation process. Feedback should be taken into account and modifications should be made. Measures that have resulted after such a process could be used in clinical trials. In order to capture meaningful changes overtime, however, it should be stressed that treatment cannot just focus on absence of symptoms but on getting patients to feel as healthy as can be, given their diagnosis. In order for this to be relevant and appropriate for different cultural contexts, the processes described need to be conducted in the same, similar settings or a range of settings. Analyses for validation, reliability are of course needed and translations should be done following appropriate methods (i.e., forward-backward translation). The WHO QOL-100 development process could be used as a reference for the outline of such a process where many stages of development were followed to develop a QoL measure, appropriate for many cultural contexts or allowing for cultural differences [https://www.who.int/mental_health/media/en/76.pdf]. Beyond the use and development of standardized questionnaires, other patient-centric approaches could also be encouraged in order to get qualitative insights based on well adopted design paradigms (e.g. "Design Thinking", User-Centred Design etc.) In addition to the collection of patient information (information flow from patients to physicians), it is important that there is information flow from physicians/scientists/researchers to patients, so that patients can be	

			adequately informed and clearly see/harvest the benefits (both personally and collectively) of the drug development processes they are involved in. We would propose also to include an outline of an action plan highlighting priorities.	
9	77		Table – (right) column: Potential ICH Guideline Topic **Comment:** The proposed content for the ICH guideline is missing considerations relating to sustainability. Once work has been done to understand which assessment measure concepts of importance to patients with a particular disease, it would be important to capture this in a way which avoids duplicating the work (and allows for modifications as needed over time).	….. guideline would include: • Qualitative and quantitative methods to identify disease/ treatment impacts important to patients that would be candidate concepts for measurement with patient reported outcome (PRO) measures or other types of COAs or in quantitative assessments of the patient perspective. **• The approach to documenting the agreed assessments (COA, PRO or other measures) for a specific disease in a sustainable way.** • The approach to organizing and structuring the content of the guideline document would…
			Table - row 2, (left)column: Patient Preferences Informing Drug Development, Benefit-Risk Assessments, and Other Decisions **Comment:** The section about "identify which treatment benefits would be most desirable to obtain" seems duplicative of the row above, where the ICH guideline would include "Qualitative and quantitative methods to identify disease/treatment impacts important to patients that would be candidate concepts for measurement with patient reported outcome (PRO)".	"What methods and approaches could be used to ~~identify which treatment benefits would be most desirable to obtain and which risks would be most important to avoid, or to~~ explore what patients might consider to be acceptable tradeoffs of increased expected harm(s) for a specified increase in expected benefit with a new medicinal product **(or decreased expected**

				harm(s) for a specified decrease in expected benefit)?"
			Table - row 2, (left)column: Patient Preferences Informing Drug Development, Benefit-Risk Assessments, and Other Decisions **Comment:** Given that ICH M4E(R2) states that benefits can include non-health benefits such as convenience, it is assumed that the same applies here. Nonetheless, shouldn't it be stated explicitly? This could be done by adding a new sentence (taken directly from ICH M4E(R2)).	… in expected benefit with a new medicinal product? **Benefits may also include important characteristics of the medicinal product, such as convenience (e.g., a more convenient dosing regimen or route of administration) that may lead to improved patient compliance, or benefits that affect those other than the patient (e.g., population benefits of a vaccine due to herd immunity).**
15	77	C	Drug development process informed by patients: other important aspects include comparator, length of placebo, access to data or to product post-trial, informed consent forms, communication about progress, burden of trial (ie, biopsies), compassionate use, retention, information on the results... The new ICH guidelines should also address practical arrangements for clinical trials	• Qualitative and quantitative methods to identify disease/treatment impacts important to patients that would be candidate concepts for measurement with patient reported outcome (PRO) measures or other types of COAs or in quantitative assessments of the patient perspective. **In addition, methodological guidelines to explore how participants can access their own data after the trial (or when leaving trial, unblinding data for a trial participant before the end of the trial without impacting the trial validity), how to inform participants on the trial itself (recruitment, retention, amendments…), about the overall trial results…**

			Patient preferences informing drug development, benefit-risk assessment, and other decisions: among other decisions, the decision made by the patients to ake the medicine, once authorised. For this, different methods to explain the benefit/risks should be tested: textual, tabular, graphic methods... (e.g. as a follow-up of IMI PROTECT project).	New ICH guideline addressing methods for elicitation/ collection, analysis, reporting and application of qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among the alternatives, **and also methods for the explanation of benefits and risks understandable by patients**
8	77-78	Table	In 'Drug Development Process Informed by Patient Perspective', it would be useful to emphasise the importance of methodology to encourage patient compliance in the second bullet.	What would be the best way to measure these disease or treatment burdens/effects in a clinical trial? And are the methods appropriate for the patients?
7	77-78	C – Table	Comment to "potential ICH guideline topic" for the Discovery/development process: The development of COAs should require mutual understanding and appreciation among the stakeholders involved. Clinical Outcomes should be not only meaningful for patients but also concord with Primary Endpoints set by the Regulator. It should be specified that COAs can be used to demonstrate clinical efficacy and/or value.	
10	82-98	1	Extremely well formulated; we undersing everything presented here.	
6	82-109	C	It should be considered that, apart from social or cultural patient sub-groups, there are also biological patient sub-groups. If we aim to include patients in the development of relevant COA etc, we should not forget that, at least for many incurable cancers, we will have an over-representation of 'long-term surviving' patients in working groups. Depending on the cancer, patients with aggressive sub-types of disease often will struggle to get involved into discussions around drug development and may have a different perspective	

			on risk/benefit ratios. This would need to be widely acknowledged and incorporated in all considerations as the risk is under-representation of patient groups with potential highest unmet clinical need.	
8	84-98		In relation to potential new ICH guidelines, one topic could be how a PRO instrument might be used to enable reliable and valid case definitions based on symptoms reported by the patients.	New guideline addressing the main characteristics of a PRO instrument that could support the identification and/or trigger of case definitions
5	86-98	C1	Methods used to develop core outcome sets might be useful when defining clinical outcome assessments (COAs). Widespread use of core outcomes sets was advocated by initiatives like: https://www.comet-initiative.org/ https://www.ichom.org/	
2	87-92	74	I think it will be important to clarify how qualitative research with patients will work relative to clinical trials, e.g., before a clinical trial in order to identify topics for clinical/quantitative research, alongside or parallel to a clinical trial, or within a multi-method clinical trial to triangulate data from both qualitative and quantitative research to arrive at more robust conclusions.	
17	97-98	C	The guideline should consider that the clinical trial endpoints should be discussed between researchers and patients at different stages of the trial, in order to yield more reliable and clinically meaningful results.	We propose the following amendment: "This guideline could include the important issue of defining clinically meaningful within-patient score changes, and collection, analysis, and interpretation **thereof, at different stages of the clinical trials and in consultation with participating or expert patients**".

5	99-109	C2	There are number of published methodological studies based on international consensus focused on the use of PROs. These publications should be consulted when developing the methods section of the ICH guideline. Reference list: SPIRIT-PRO – Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols. The SPIRIT-PRO Extension – https://www.spirit-statement.org/wp-content/uploads/jama_Calvert_2018_sc_170006.pdf CONSORT-PRO – Reporting of Patient-Reported Outcomes in Randomized Trials. The CONSORT PRO Extension - https://jamanetwork.com/journals/jama/fullarticle/1656259 SISAQOL – International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium – https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30790-9/fulltext SISAQOL – Moving forward toward standardizing analysis of quality of life data in randomized cancer clinical trials – https://doi.org/10.1177%2F1740774518795637 SISAQOL – Analysing data from patient-reported outcome and quality of life endpoints for cancer clinical trials: a start in setting international standards – https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(16)30510-1/fulltext PROTEUS Consortium promotes tools to optimize the design, analysis, reporting, and interpretation of PROs in clinical trials – https://more.bham.ac.uk/proteus/	
			Frameworks developed using the FDA guidance for Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labelling Claims	

			might be useful to stimulate discussion about methodological issues around the use and development of PROs: Clinical outcome assessments – Beyond study participants: a framework for engaging patients in the selection or development of clinical outcome assessments for evaluating the benefits of treatment in medical product development – https://link.springer.com/article/10.1007%2Fs11136-017-1577-6 PRO use in clinical trials – Patient-Reported Outcomes to Support Medical Product Labeling Claims: FDA Perspective – https://www.sciencedirect.com/science/article/pii/S1098301510606377?via%3Dihub – Content Validity – 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 - https://www.sciencedirect.com/science/article/pii/S1098301511033213?via%3Dihub	
9	104		It would be worth to clarify the scope to capture both within and outside of clinical trials that would be used for evidence generation supporting registration purpose (e.g., as preliminary input such as qualitative interviews or as real world patient preference studies).	
9	106-109		We are highly supportive of and encourage broad stakeholder engagement from patients to health technology assessment (HTA) bodies throughout the development of the guidelines to promote efficient PFDD data collection, analysis, and application. It is suggested to modify the text as proposed.	The guidance could articulate methodological requirements to design and conduct patient preference studies that would be of sufficient rigor and quality to inform drug development, **and** regulatory decision making, ~~and other health authority or health care decision makers~~ about what attributes are important ~~to patients~~, how important

				they are, and what trade-offs patients are willing to make between attributes.
17	106-109	C	Clinical trials often lead to results that were not anticipated. Such results should be communicated to and discussed with patients, in the context of an additional/second patient preference study at a late stage of the clinical trials. This updated study should then be included in the market authorisation application presented to regulatory bodies.	We suggest the following amendment: "The guidance could articulate methodological requirements to design and conduct patient preference studies **at different stages of each clinical trial** that would be of sufficient rigor and quality to inform drug development and regulatory decision making about what attributes are important to patients, how important they are, and what tradeoffs patients are willing to make between attributes."
4	109-110		An additional section belonging to § 2 should be added to address an important current challenge in EU.:	A part of § 2 to be added: "The increasing use of devices to measure/monitor patients in a decentralised manner requires a close collaboration and allignment between the Eurpean Medicines Agemcy (EMA) and the Notified Bodies (NBs) as well as a clear share of responsibilities and reuirements in the overall approval pprocess of data of patietn perspectives obtaiend through a device.
10	111-114	2	It is of utmost importance that also the regulatory authorities are involved in the drug development process at an early stage. They, in many societies, represent the funding of drug treatment. For a patient, effectiveness of the treatment matters, for the payer cost-effectiveness.	
16	115-117		It should not require a whole new circus on top of the existing activities around drug development. (see before). In COVID times you need a more	Address the organisational changes to permit immediate start of this project. Maybe it should not be a project by a more

			directive approach. The industry should pay for this new research at the expense of present in company research,	radical paradigm shift in the way drug development is conducted.
4	117	7	The need for an outline of a standardized approach of identifying, collecting and analyzing prioritised, relevant patient perspective including defining a meaningful change are suggested to start after substantial completion of related ongoing work. This can cause huge time delays not serving the high need for the:_ * patients to take their prioritised perspectives into account as well as * pharmaceutical industry to increase their success of a new medicine.	change to "t*hat the outlined work should be started soonest possible in* *parallel with completion of the related ongoing ICH work. Avoidance of* *any duplication of content should be carefully ensured",*
5	123-129	D	Patient and public involvement (PPI) is essential in the development and conduct of PRO research. The research protocol should include PPI. The research publication should state how PPI was used throughout the research. It's also important that the extent to which translated and culturally validate PROMs are used in clinical trials should be clear. Reasons for not including wider ethnic groups should be made transparent in protocols and publications. It is also important that ethnic groups are included in the development of PROMs. A paper by Dr A.L. Slade entitled "Systematic Review of the Use of Translated Patient Reported Outcome Measures in Cancer Trials" (currently under review by BMC Trials) found that minority groups are underrepresented in cancer trial research where PRO were used as primary or secondary outcomes. The review found that ethnicity groups were not reported and the extent to which translated and culturally appropriate measures were used to capture PRO data was not transparent. Few trials reported collection of data by ethnic groups despite many of the studies being multi-centered and multi-national. Secondly, none of the trials including the multinational studies reported using translated PROMs, although participants stated in qualitative interviews that they were used. This was not clear in either the protocols or published	

			papers. Qualitative interviews highlighted significant barriers to the use of translated and culturally validated PROMs, including: availability of measures; insufficient resources and training; investigator burden; and administrative difficulties associated with collecting different versions. The dearth of reporting in both protocols and publications raises several issues and questions: 1) The extent to which patients were excluded because of language barriers was not transparent, 2) The extent to which translated and culturally validated PROMs were being used was not clear, as it was not reported in protocols or publications. This raises concerns that data collected in clinical trials is under representative of ethnic minorities and results may not be applicable to all ethnic groups. This is especially important as ethnic groups often present later and with more advanced health problems. Moreover, following paper provide important insight into PPI: "Give Us The Tools!" - Development of knowledge transfer tools to support the involvement of patient partners in the development of clinical trial protocols with patient-reported outcomes (PROs), in accordance with SPIRIT-PRO Extension (currently in press by BMJ Open) Moving beyond project-specific patient and public involvement in research - https://journals.sagepub.com/doi/10.1177/0141076819890551	
11	123-129	D	The specifics on "how" is most important here, thus input on the guidelines proposed as next steps will be crucial.	