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ICH reflection paper on proposed ICH guideline work to advance patient focused drug Development

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ICH Reflection paper

Proposed ICH Guideline Work to Advance Patient Focused Drug Development

Under public consultation until 7 March 2021

This paper identifies key areas where incorporation of the patient's perspective could improve the quality, relevance, safety and efficiency of drug development and inform regulatory decision making. It also presents opportunities for development of new ICH guidelines to provide a globally harmonized approach to inclusion of the patient's perspective in a way that is methodologically sound and sustainable for both regulated industry and regulatory authorities.

A. Background

Patients have direct experience in living with a disease. 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.

Growing patient advocacy and patient engagement, and continued advances in communication technologies, internet, social media, and a proliferation of information services and sources, have created a rich yet complex environment for eliciting and incorporating patient perspectives throughout the drug development process. In this environment it is increasingly critical to develop a harmonized approach to collecting and incorporating patient perspectives in drug development and decision making.

In many instances patient focus is already considered in traditional development plans, and patient input, when needed, is already sought except that the methods for identifying, collecting, and analyzing 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.

If methodologically-sound data collection tools are developed and used within clinical trials, and sound standards for the analysis, reporting and application of the results are developed and used, patient input can provide a valuable direct source of evidence regarding the benefits and risks of a drug including, where needed, relevant information on patient preferences.

Throughout the drug development process there is an opportunity to increase the quality of the development program through effective inclusion of the patient's perspective. These opportunities include but are not limited to: understanding the clinical context for medicines development and evaluation; product design features including formulation and delivery modes that minimize burden and support adherence; development of endpoints that reflect benefits that matter most to patients and which adverse event endpoints are most important for patients; designing trials that support better enrollment and retention; informing regulatory decision making including patient acceptability of benefits vs risks vs tolerability concerns, and effective risk management.

To maximise the benefit of patients' perspectives in these areas, regulators and drug sponsors need to employ methods and measures that:

- ensure the information collected is of sufficient reliability, validity, and representativeness to be used as a basis for planning and decision making,
- can be deployed in a timely and sustainable way,
- will be relevant to patients (and their caregivers) living with the same disease in multiple regions of the world, and reflect concepts (e.g., pain, fatigue, physical function, etc.) that matter and measure changes that would be meaningful, and
- account for heterogeneity or subgroups.

This reflection paper identifies a series of drug development and regulatory decision-relevant questions that arise during the drug development process and proposes potential guideline work for ICH to outline methods and standards to be applied when collecting and incorporating patient perspectives to address these questions.

B. Incorporating Patient Experience to Better Inform Drug Development and Regulatory Decision Making

Throughout the drug development process, patient perspectives can be valuable in addressing specific questions to inform development programs and related regulatory decision making. For example:

Questions in the discovery and development phase may include:

- What are patients' unmet needs that suggest potential drug targets?
- What disease effects and treatment burdens matter most to patients that might be addressed by a medical therapy? (How) does this vary by subpopulation?
- What would be the best way to measure these effects?
- 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?
- What is a clinically meaningful change in an endpoint from a patient perspective?
- How to define meaningful change in a patient over time?

Questions related to patient preference—relevant throughout development—could include:

- What methods and approaches could be used to identify, for example, 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?
- What are methodological considerations for sponsor conduct of patient preference studies to provide credible and reliable findings to support regulatory decision making?

The above questions are not meant to be exhaustive, but rather are meant to convey that there is a range of opportunities for informing development and decision-making, and some of the research methods that would be applied are relevant to address more than one of these questions.

C. Proposed Topics for future ICH Guideline Development supporting Patient Focused Drug Development

The table that follows offers a mapping from the questions posed above to potential topics for new ICH guideline work.

Drug Development Process Informed by Patient Perspective	Potential ICH Guideline Topic
Discovery/ Development: • What disease effects and treatment burdens matter most to patients that might be addressed by a medical therapy? (How) does this vary by subpopulation? • What would be the best way to measure these disease or treatment burdens/effects in a clinical trial? • What would be the most appropriate endpoints to use in clinical trials (and robust enough to inform regulatory decision making)? • What is a clinically meaningful changes in an endpoint from a patient perspective? • How to define meaningful change in a patient over time?	**New ICH guideline** addressing what to measure in a clinical trial, including refining the set (list) of important impacts and concepts from patients, to select, modify or develop clinical outcome assessments (COAs) that can demonstrate change, defining endpoints, and meaningful change. The scope of this 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 organizing and structuring 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.
Patient Preferences Informing Drug Development, Benefit-Risk Assessments, and Other Decisions: • 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? • What are methodological considerations for sponsor conduct of patient preference studies to provide credible and reliable findings to support regulatory decision making?	**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.

As drug sponsors increasingly collect and wish to include patient experience data as part of the dossier submitted to regulatory authorities, there may also be opportunities to revise ICH M4E and ICH M8 to harmonize regulatory requirements for reporting and submission of these data.

Some additional considerations for what might be included in the proposed new guidelines:

1. **New ICH guideline addressing what to measure in a clinical trial, including refining the set (list) of important impacts and concepts from patients, to select or develop fit-for-purpose**

clinical outcome assessments (COAs) that can demonstrate change, defining endpoints, and meaningful change.

This guideline could address methods for refining the list of important impacts and concepts from patients to develop potential study instruments. Given that not everything identified as important by patients, caregivers, and clinicians is measurable and/or can demonstrate change in a specific treatment trial, the guideline would address how one would select what to measure for the purposes of a drug development program to show clinical benefit, and how one might identify, modify or develop fit-for-purpose COAs that may include patient reported outcome (PRO) tools to assess outcomes of importance to patients. As noted in the table above, the proposed guideline would not only address design, development or selection of PROs but also include other COA types that may be appropriate for a given concept and clinical context or patient population such as observer reported (ObsRO), clinician reported (ClinRO), performance based measures (PerfO), or others.The guideline could also consider, given the selection of a COA measurement tool and data collection approach, how an appropriate clinical trial endpoint could be determined. This guideline could include the important issue of defining clinically meaningful within-patient score changes, and collection, analysis, and interpretation.

2. **New ICH guideline addressing methods for elicitation or collection of assessments of the relative desirability or acceptability to patients of specified alternative outcomes or other specified alternative attributes.**

This guidance could address methods for robust reliable capture of information about the value that patients place on aspects of medical treatment that can help account for differing patient perspectives on benefits,risks and tolerability issues. In addition, it may also reflect their experience with disease, stage of disease progression, other life circumstances, and cultural and religious beliefs, for example. 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 about what attributes are important to patients, how important they are, and what tradeoffs patients are willing to make between attributes.

D. Topic Sequencing, Timing and Other Considerations

It is noted that there are existing regulatory guidances, a number of ongoing collaborative efforts, and a large body of existing literature that would support the development of these proposed guidelines.The two new guideline topics identified are considered priority areas for the advancement of more "patient focused" drug development, and they are presented in what is considered to be priority order.

Recognizing the limited staff capacity in regulatory authorities and companies having the requisite expertise in psychometrics, related statistics, and decision sciences to undertake this work it is suggested that the outlined work be considered to start after substantial completion of related ongoing work.[1]

Following review, discussion, and potentially further revision of this paper to reflect the perspectives of other ICH Assembly members, the potential endorsement of this reflection paper would be considered. If the reflection paper and associated body of potential future work is endorsed, the timing

[1] Other ongoing work includes for example, FDA, United States' development of a series of Patient Focused Drug Development guidance required under the 21st Century Cures Act https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical and the IMI PREFER project: https://www.imi-prefer.eu/.

of submission of any of these new topics (or others that may be identified by ICH members) through the annual new topic process can be further considered.

A harmonized approach to collecting and incorporating patient perspectives in drug development and decision making will provide significant efficiency benefits, but regional and/or cultural differences may limit direct transferability of the results. Therefore, to mitigate this potential challenge, the process of developing these methodological guidelines should consider including the development of a harmonized acceptable approach for how to assess applicability across regions and/or cultures, perhaps in a manner similar to how the ICH E5 Ethnic Factors in the Acceptability of Foreign Clinical Data addressed extrinsic factors (e.g., cultural and environmental).

Finally, ICH notes a challenge that is anticipated and will need to be addressed concerning the practical involvement of stakeholders in this topic/process. In view of this the following next steps are being undertaken:

- This PFDD Reflection Paper is posted on the ICH website to allow for public comment similar to the approach taken for the ICH GCP Renovation Reflection Paper.
- If the proposed guideline work is advanced in new topic proposals and is subsequently endorsed by the the ICH Assembly, the new topic concept paper and business plan should include plans for public consultation and engagement similar to the approach being taken for ICH E6(R3), incorporating the learnings and best practices from that E6(R3) experience.