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To: United States Food and Drug Administration (FDA)

From: International Society for Quality of Life Research (ISOQOL) Mixed Methods (MM) Special Interest Group (SIG)

Date: November 2019

Subject: Patient-Focused Drug Development Guidance 2—*Methods to Identify What Is Important to Patients*

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We commend the FDA (henceforth, “the Agency”) for drafting the second in a series of four planned methodological guidance documents on patient-focused drug development (PFDD). The draft guidance published by the Agency in October 2019 clearly outlines a variety of methods to understand and identify what matters most to patients regarding the burdens of disease and treatment to guide medical product development. This document will be an important resource to all stakeholders involved in drug development to inform the selection or development of clinical outcome assessments and the generation and submission of patient experience information to the Agency for consideration.

## Introduction

This memo has been drafted collaboratively by members of the ISOQOL Mixed Methods (MM) special interest group (SIG). The purpose of the ISOQOL MM SIG is to promote the use of MM research in the field of health outcomes research by exploring the challenges and methodological solutions offered by this research paradigm, identifying opportunities for application of MM research in the field, and defining good practices. Our ultimate aim is to share and learn best-practice methodologies that can be utilized to enhance the patient-centeredness of health outcomes research.

Collectively, the ISOQOL MM SIG members reviewed the Draft Guidance, *Patient-Focused Drug Development—Methods to Identify What Is Important to Patients* and developed the following recommendations for consideration.

## General Comments on Mixed Methods

- **Definition:** In the draft guidance, the MM research is described as “*research that used both qualitative and quantitative methods*”. This definition is too simple to be accurate and could lead to some confusion. For example, it could describe an approach where quantitative and qualitative components address different research questions, an approach where results from independent qualitative and quantitative researches are simply collated or a “multi-method approach” in which there is no integration phase for the qualitative and quantitative components. We would like to highlight that the *integration* of qualitative and quantitative methods is integral to mixed

methodology which we missed in the definition proposed and would recommend using the widely accepted definition by Tashakkori and Creswell: “*Mixed Methods Research is a research in which the investigator collects and analyses data, integrates the findings, and draws inferences using both qualitative and quantitative approaches or methods in a single study or program of inquiry*”<sup>1</sup>

- **References:** We recommend including references that could help stakeholders with understanding and designing MM measurement studies. The MM SIG developed a position paper that outlines a process for incorporating MM in health outcomes research to guide researchers in their efforts of conducting good quality MM research. This paper outlines the benefits and challenges of MM, describes the types of support needed for designing and conducting robust MM measurement studies and proposes a framework to guide researchers in their MM research endeavors.<sup>2</sup> We outlined the following three defining components of MM research:
  - Clear specification of the single research question that will be addressed using both qualitative and quantitative components (data/methods),
  - Purposely and prospectively defined quantitative and qualitative components in a well-defined, pre-specified research design,
  - Integration of the evidence generated by both the quantitative and qualitative components of the research.

Moreover, the ISOQOL MM SIG is currently conducting a scoping review that aims at reviewing MM designs, applications, and methods in health outcomes research. Dissemination of the results of this work is planned for 2020.

## Specific Comments on Mixed Methods Section

- **Mixed Methods:**

The draft guidance is not prescriptive in terms of design or method, which we believe is a good thing. The section on MM (pp. 15-17, lines 367–411) provides a good high-level overview of the rationale and reasons for using MM. The typology of purpose for MM research (triangulation, complementarity, initiation, and expansion) and the description of key aspects of MM research design (predominance of one strand of research over the other, sequential/parallel application of the strands of research) is well explained and useful. However, the notion of exploratory vs. confirmatory research is somehow missing. Moreover, additional information on the value of MM, the strengths and limitations of this approach as well as potential applications in the context of clinical setting would be beneficial for researchers.

- **Populations:**

We recommend that the Agency provides additional further clarifications on MM data collection technique. In MM research, it is not necessary that qualitative and quantitative streams involve data collected with the same patients. The MM design may combine qualitative and quantitative

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<sup>1</sup> Tashakkori, A., & Editorial, C. J. W. (2007). The new era of mixed methods. *Journal of Mixed Methods Research*, 1, 1–6.

<sup>2</sup> International Society for Quality of Life Research (ISOQOL) Mixed Methods Special Interest Group (SIG). Towards the use of mixed methods inquiry as best practice in health outcomes research. *J Patient Rep Outcomes*. 2017;2(1):19.

data from different samples of patients to address a single research question – Patients could be clinical trial participants or non-clinical trial participants. The design and specification of MM are driven by data collection process, not by the analysis technique. The ability to make this clarification will further highlight the robustness and utility of MM in health research and clinical trials.

- **Examples of Mixed Methods Designs:**

The Agency provides three useful examples of MM research using different designs e.g. qualitatively driven concurrent design, quantitatively driven sequential design and equal status sequential design. However, there is no or little background on these examples and the reason they are chosen is not made explicit. The guidance does not clearly state that other MM approaches would also be acceptable and could be used in the context of clinical research. For instance, embedded MM clinical research designs using longitudinal interviews with clinical trial participants is particularly useful to understand the effects of an intervention on the patient experience, explore meaningful changes which may occur over time and understand the processes associated with these changes. This approach limits potential recall bias or the failure to recall previous events or experiences accurately. Longitudinal interviews can be conducted with a subset of clinical trial participants at different time points to provide evidence of treatment benefit from the patient’s perspective and support the interpretation of meaningful changes in clinical and PRO outcomes. The ISOQOL MM SIG is currently leading a program that aims to promote the use of longitudinal qualitative data collection in health outcome research and define best-practice methodologies. Dissemination of the results of this work is planned for 2020.

A more systematic approach of the examples, using a clearly defined framework (as defined above) would certainly be useful and would acknowledge more efficiently the diversity of all possible MM research solutions.

- **Integration of evidence**

The challenges of integrating qualitative and quantitative evidence, especially in the case of discrepant findings should also be acknowledged. It is worth noting that approaches for resolving and reconciling discrepant or contradictory findings can pose significant challenges to researchers. The resolution of conflicting or discrepant findings should be guided by both the context and purpose of the initial investigation. One possibility is to state that one set of findings may be “prime” compared to the other or to state that conflicting or discrepant findings are possible and constitute an area of further investigation. This integration should be anticipated as much as possible at the research design stage.

- **Sample size consideration**

Given that sample size can be a critical issue in clinical trials, the Agency can include the usefulness of MM in cases of inadequate statistical power, for example in rare diseases or underpowered studies. Embedded samples, where qualitative data is collected from a subsample of a larger quantitative sample is a prime example of this.<sup>3</sup> A specific section on sampling method in MM could be useful.

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<sup>3</sup> Wisdom J, Creswell JW. Mixed methods: integrating quantitative and qualitative data collection and analysis while studying patient-centered medical home models. *Rockville: Agency for Healthcare Research and Quality*. 2013.

## Proposed Revisions/ Clarifications if Any

Proposed Revision	Location/Comment
<p>“this methods described in this document can be use ...[...] and the generation and use of <i>patient preference information</i>.”</p> <p><i>Patient preference data not discussed in this guidance. Should be replaced by patient experience data.</i></p>	Line 62-64
Mixed methods Research involves the <i>integration</i> of qualitative and quantitative data	Line 109 & 371
We would recommend adding sampling method (i.e., purposive sampling, maximum variation sampling) to considerations for qualitative research in order to meet the requirements of the define research question	Page 5
Clarify that the sample size estimated prior to the study will likely not match the final sample size. This is to encourage regulatory bodies to allow for flexibility in ‘recruitment targets’ and facilitate qualitative research in the clinical trial environment.	Line 143

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