European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

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Stakeholder Survey on the ENCePP Code of Conduct

Final Report

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Introduction

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) was set up in 2008 to strengthen methodological standards, transparency, and scientific independence aimed to support the evaluation of medicines in Europe (1). The ENCePP Code of Conduct, referred to hereafter as the Code, was first released in 2010 to set out a framework for good practice in the relationship between investigators and study funders, irrespective of whether the study funder was a public body, industry or a regulatory authority, to address the influence of the funding source on the interpretation and publication of results of pharmacoepidemiological studies (2). The purpose was ultimately to improve public confidence in the integrity of pharmacoepidemiological research, for the benefit of all parties involved - researchers, industry, regulators and the public. In March 2018 the fourth revision of the Code was published.

A survey of stakeholders was conducted to evaluate how potential users understand and would apply the revised Code in practice. In this report the survey and its results are described and discussed.

Methods

Five categories of stakeholders were identified: patient and consumer organisations, healthcare professionals, pharmaceutical industry, public health body or regulators, and researchers (academic, contract research organisations and other type of research professionals not employed by pharmaceutical industry).

The questions were developed to test the respondents on the following five dimensions:

- Usefulness: for which types of studies the Code was considered to be beneficial
- Clarity: whether the Code was considered to be clear
- Trust: whether application of the Code was increasing trust in a study
- Participation: whether the respondent felt a higher propensity to participate in a study if compliant with the Code
- Redundancy: whether the Code was perceived as redundant with respect to other guidelines

The respondent was first asked to self-assign a stakeholder category. For some dimensions, the questions were adjusted by stakeholder category to match their perspective and expected level of expertise in the field of non-interventional post-authorisation studies. As a consequence, stakeholder categories were grouped for the analysis of responses where indicated. The full questionnaire is available as supplement.

The survey was conducted with the EU Survey® tool and a web-link to the online survey distributed to stakeholders of the European Medicines Agency (EMA) via established communication channels. ENCePP members were also requested to share the web-link with other members in their organisation. The survey was launched on June 1st 2018 for the duration of one month.

Results

Description of respondents

The total number of respondents was 87. Figure 1 shows the breakdown in categories of stakeholders: 6 (6.9%) were in the category '*patient and consumer organisation*' (PAT), 10 (11.5%) in the category '*healthcare professional*' (HCP), 16 (18.4%) in the category '*pharmaceutical industry*' (PHARMA), 12 (13.8%) in the category '*public health body or regulator*' (REG), and 43 (49.4%) in the category '*researcher*' (RES).

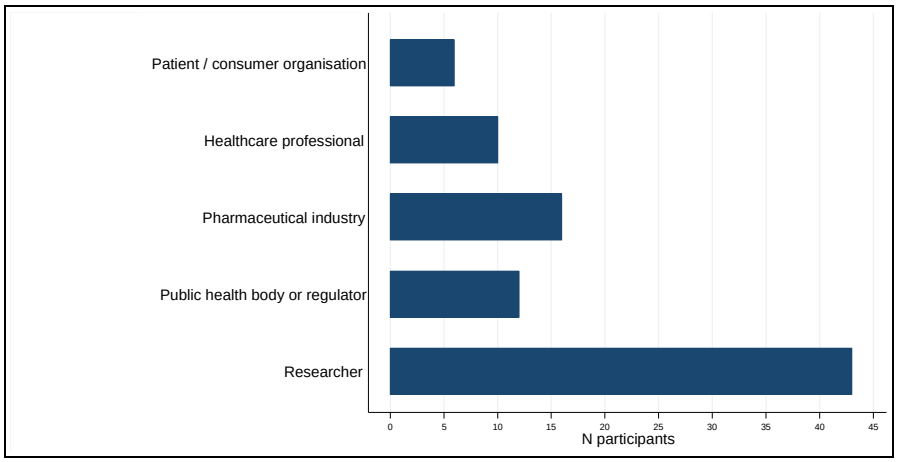

Figure 1: Respondents broken down by stakeholder category.

Responders mostly assessed their knowledge about non-interventional post-authorisation studies as '*fairly good*' (33, 37.9%) or '*expert*' (31, 35.6%). Figure 2 shows a break-down of responses by stakeholder category. As expected, most of the respondents in PHARMA, PUB and RES categories self-rated their knowledge above average, while those in PAT and HCP categories assessed their knowledge mostly as average or below average.

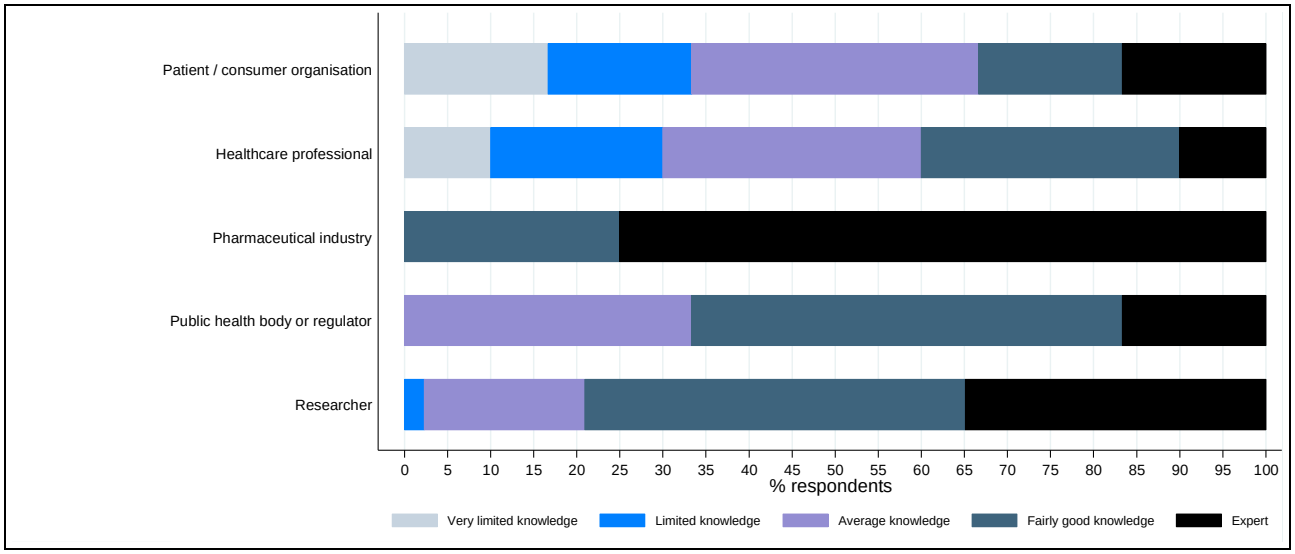

Figure 2: Answers to the question '*How would you rate your level of knowledge about non-interventional post-authorisation studies?*', by stakeholder category.

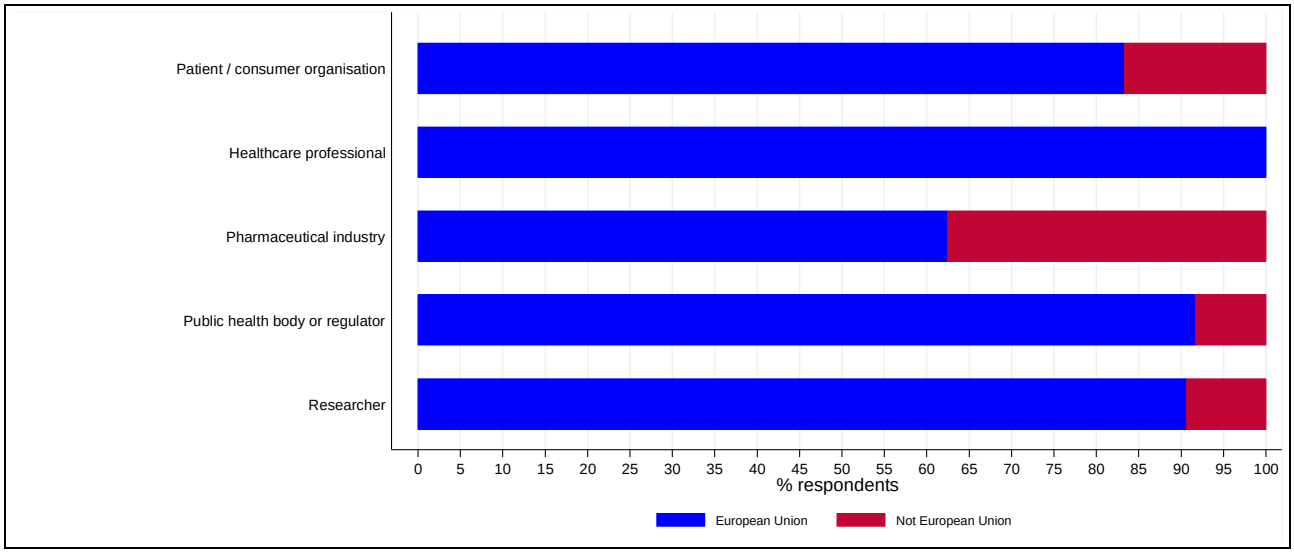

Figure 3: Area of residence of respondents by stakeholder category.

The majority of respondents (75, 86.2%) were from countries of the European Union (EU), mostly France and Germany (12 each), Italy (9), and Spain (8). Figure 3 shows that the majority of respondents from outside the EU were in the PHARMA category.

Dimension 1: usefulness

The dimension of usefulness was addressed by presenting a list of types of studies and asking to mark those where the Code was perceived as being beneficial. The list was different per PAT and HCP, on one hand, and per REG, PHARMA and RES, on the other, due to expected different levels of expertise. Responses from PAT and HCP were analysed separately from responses from REG, PHARMA and RES.

The list presented to PAT and HCP contained 9 items. Among them, item #3 '*All studies regardless of the use of their results. Scientific independence and transparency should be ensured systematically*' and item #7 '*All types of studies if study results are intended to be used for any official decision on a medicinal product (including pricing and reimbursement or influencing healthcare policies*)' were those marked by the highest number of respondents (11, 78.5%), in particular all the respondents in PAT marked the former (Figure 4). One HCP (6.2% of the PAT and HCP respondents) marked item #8 '*I am not convinced applying the Code would add value to any type of study*'. Figure 4 shows the responses per respondent category.

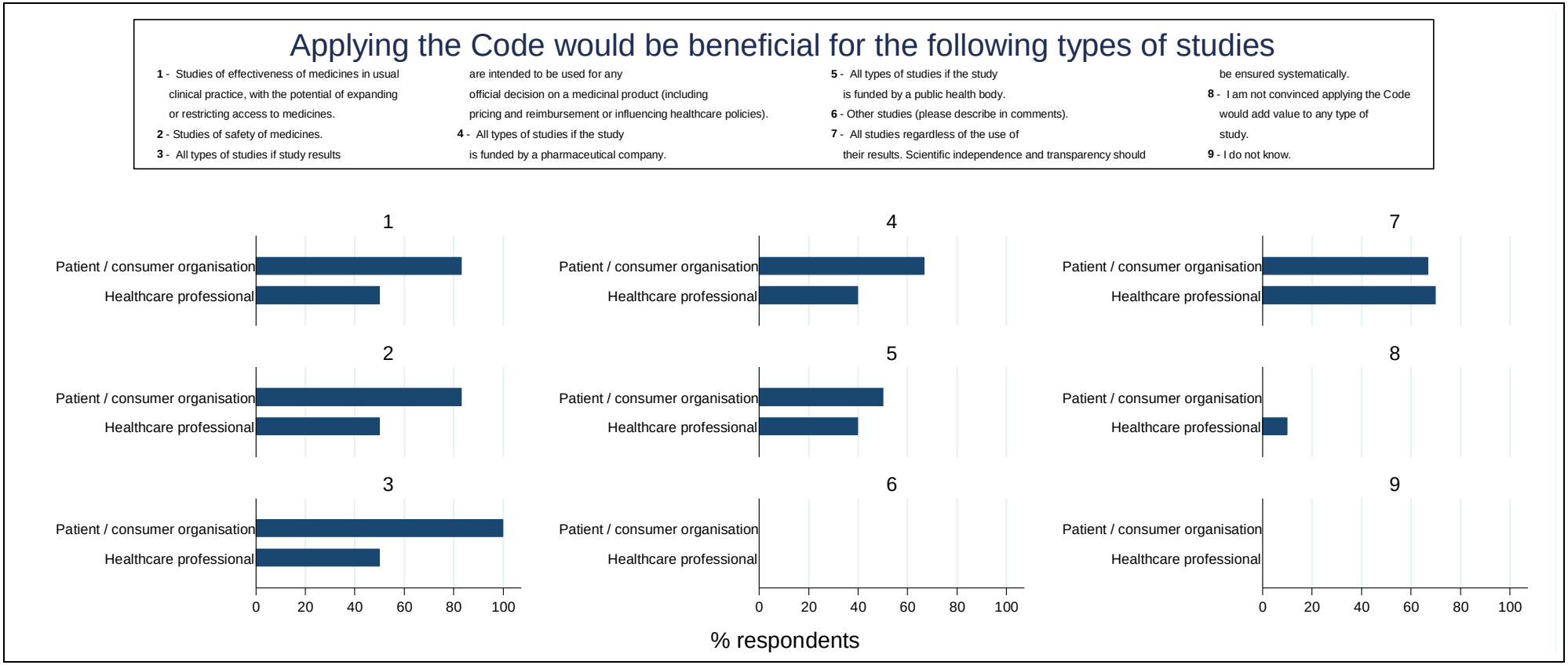

Figure 4: Choices in the list of items proposed to PAT and HCP for the question '*Applying the Code would be beneficial for the following types of studies*', by stakeholder category (n=16 responders with multiple answers).

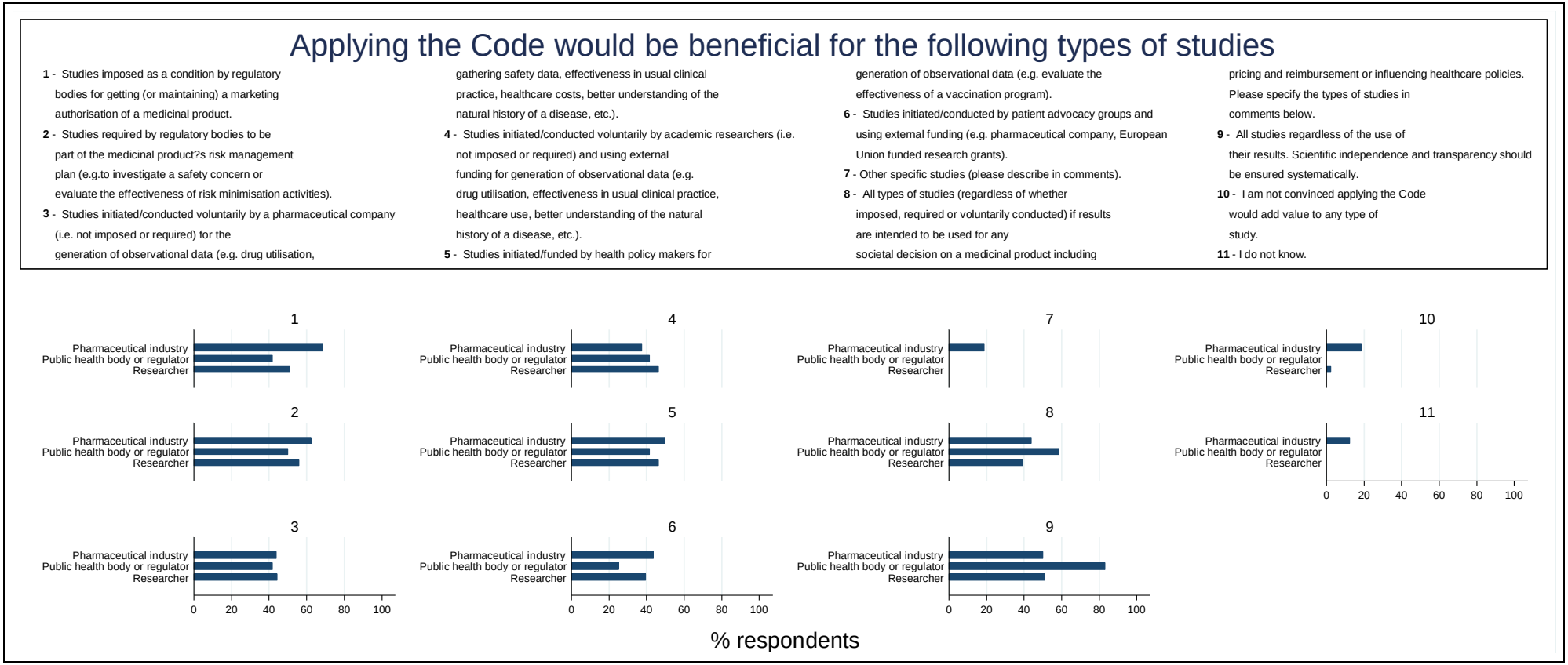

Figure 5: Choices in the list of items proposed to PHARMA, REG and RES for the question '*Applying the Code would be beneficial for the following types of studies*', by stakeholder category (n=71 responders with multiple answers).

In the list of 11 items proposed to PHARMA, REG and RES, item #2 '*Studies required by regulatory bodies to be part of the medicinal product's risk management plan (e.g. to investigate a safety concern or evaluate the effectiveness of risk minimisation activities)*' and item #9 '*All studies regardless of the use of their results. Scientific independence and transparency should be ensured systematically*' were marked by the highest number of respondents (40, 56.3%), and item #1 '*Studies imposed as a condition by regulatory bodies for getting (or maintaining) a marketing authorisation of a medicinal product*' was also marked by the majority of respondents (38, 53.2%).

Figure 5 shows that the items were rated fairly consistently by respondents in the PHARMA and RES categories. REG chose more often item #9 and item #8 '*All types of studies (regardless of whether imposed, required or voluntarily conducted) if results are intended to be used for any societal decision on a medicinal product including pricing and reimbursement or influencing healthcare policies*', and less often item #6 '*Studies initiated/funded by health policy makers for generation of non-interventional data (e.g. evaluate the effectiveness of a vaccination program)*'. Item #1 was chosen by PHARMA more often than by RES or REG.

Three in PHARMA and one in RES (4 respondents, 5.6% of this group of respondents) marked item #10 '*I am not convinced applying the Code would add value to any type of study*'.

Dimension 2: clarity

The dimension of clarity was assessed separately for PAT and HCP, and for REG, PHARMA and RES.

Stakeholders in PAT and HCP were asked two questions. The first question referred to a new section in the Code and the understanding of the principles of scientific independence and transparency. The vast majority of the 16 respondents in this group (14, 87.5%) answered '*Yes likely*' or '*Yes definitely*', and the remaining answers were 'Average'. Figure 6 shows the distribution of answers per category.

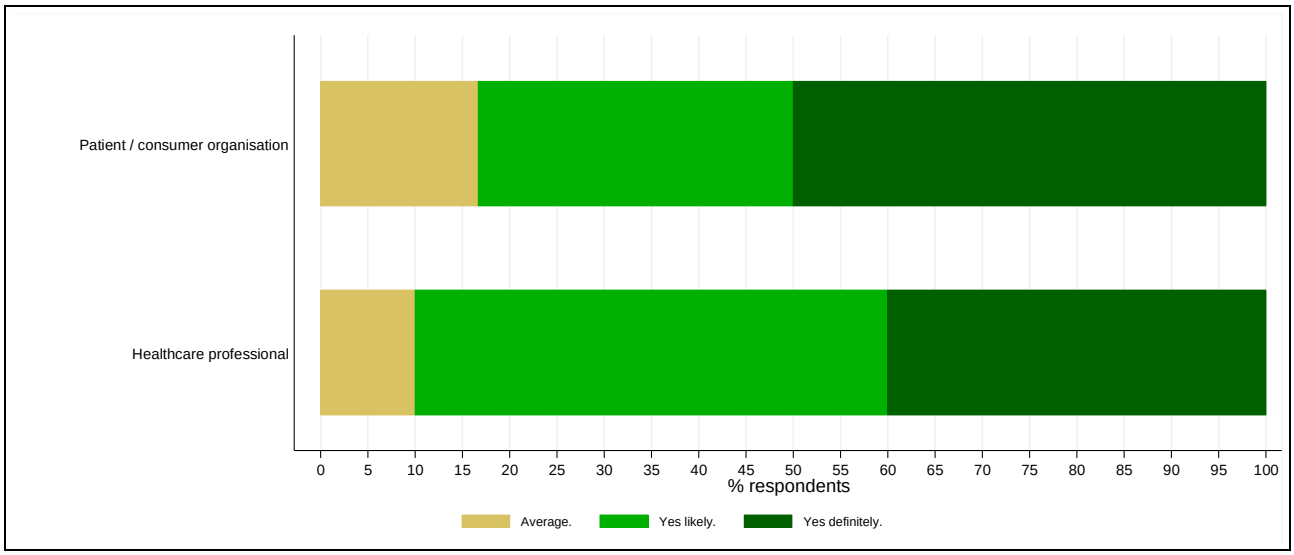

Figure 6: Answers to the question '*Do you understand what is meant by the principle of scientific independence and transparency in a study (see chapter 3.1 and 3.2 of the Code)?*' by stakeholder category among those who received the question.

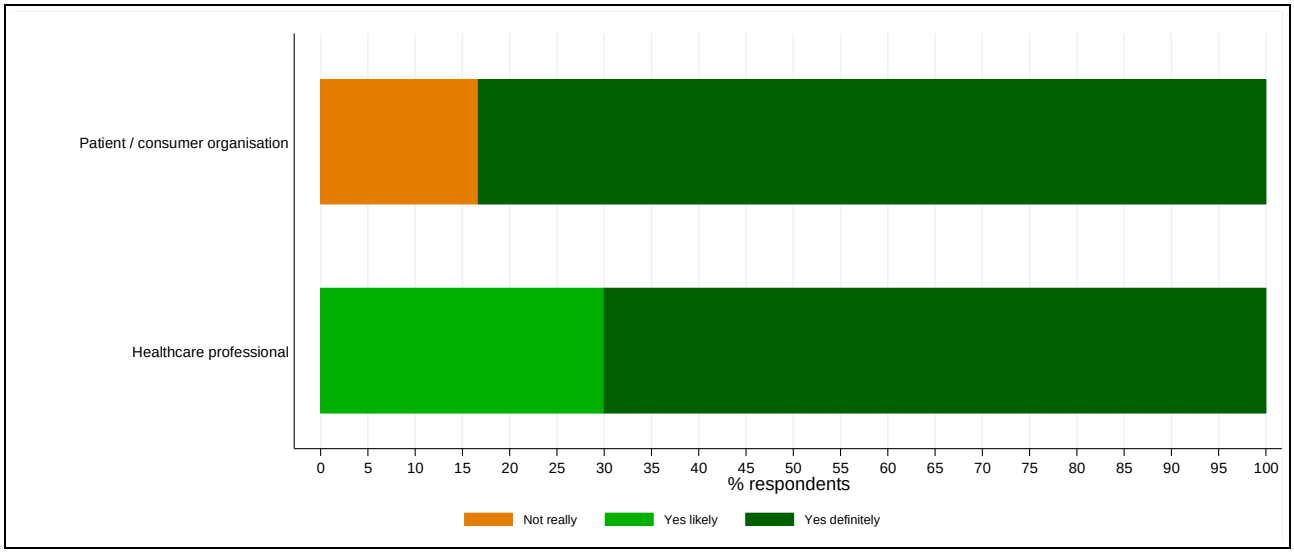

Figure 7: Answers to the question '*Do you find the principle of scientific independence and transparency important?*' by stakeholder category among those who received the question.

The second question asked participants to rate the importance of these two core principles. Again the vast majority (15, 93.7%) answered '*Yes likely*' or '*Yes definitely*', but there was one respondent in the PAT category (see Figure 7) who gave a mildly negative answer ('*Not really*').

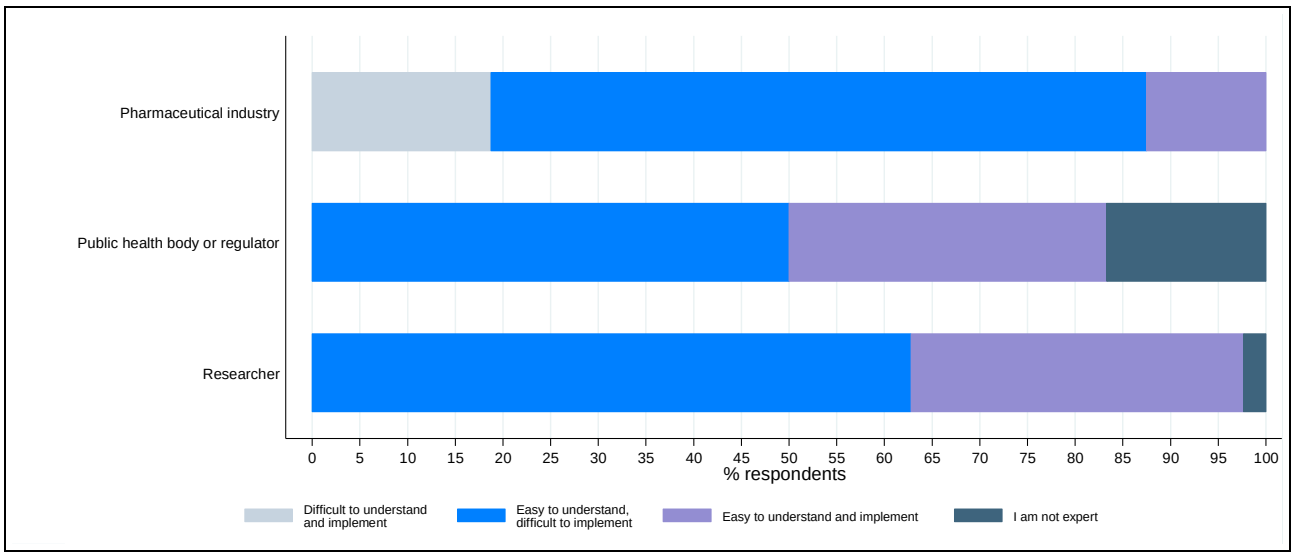

Figure 8: Answer to the question '*The principles and rules of the Code seem to me:*', by stakeholder category among those who received the question.

Stakeholders in the categories PHARMA, REG and RES were asked a single question in the dimension of clarity: whether the Code seemed easy or difficult both to understand and to implement. The majority (44, 62.0%) found it easy to understand but difficult to implement, while 21 (29.6%) rated it as easy on both dimensions. Figure 8 shows the answers broken down per stakeholder category. The only respondents who found the Code difficult both to

understand and to implement were in the PHARMA category (3 respondents). Two respondents in REG and one in RES rated themselves as not expert enough to answer the question.

Dimension 3: trust

To investigate the dimension of trust, all the respondents were requested to comment the statement '*Studies applying the Code would reinforce my trust in the study results*'. The vast majority (73, 83.9%) replied '*Yes definitely*' (34, 39.1%) or '*Yes likely*' (39, 44.8%). Figure 9 shows that the 5 mildly negative answers '*Not really*' were scattered across HCP (one respondent), PHARMA (two respondents) and RES (one respondent), and that HCP was the category with the higher prevalence of non-positive answers: beyond the one giving a negative answer, 3 responded '*Average*', for a total of 4 respondents (40% in this category). Among PHARMA were 5 (31.2%) non-positive answers.

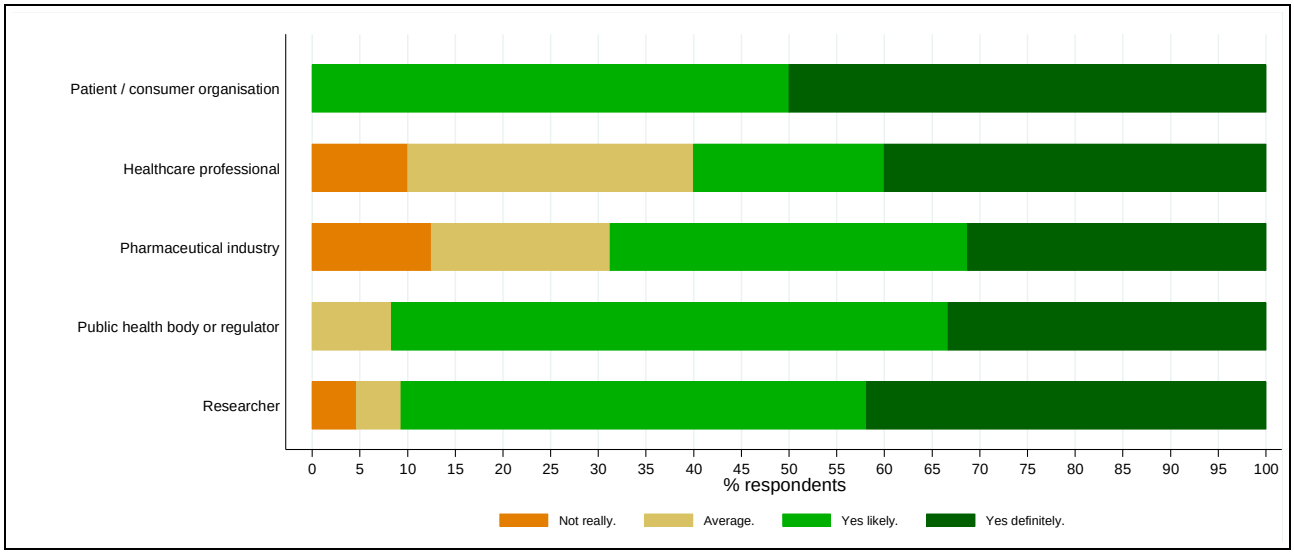

Figure 9: Answers to the question '*Studies applying the Code would reinforce my trust in the study results*', by stakeholder category.

Dimension 4: participation

Participants were requested to rate whether they felt a higher propensity to participate in a study if it was compliant with the Code. Each category received a different question, according to the role in the study implied by the category: for PAT, as study subject; for HCP, as investigator; for PHARMA, as a funder; for REG, as a funder or investigator; for RES, as a researcher. The answers are represented in Figure 10. In all stakeholder categories the majority of respondents gave a positive answer '*Yes definitely*' or '*Yes likely*': in REG 11 (91.7%), in PAT 5 (83.3%), in RES 33 (76.6%), in HCP 7 (70.0%) and in PHARMA 8 (50.0%). In all categories but REG there were some negative answers '*Not really*' or '*Not at all*': in HCP 2 (20.0%), in PHARMA 3 (18.7%), in PAT 1 (16.7%) and in RES 6 (13.9%).

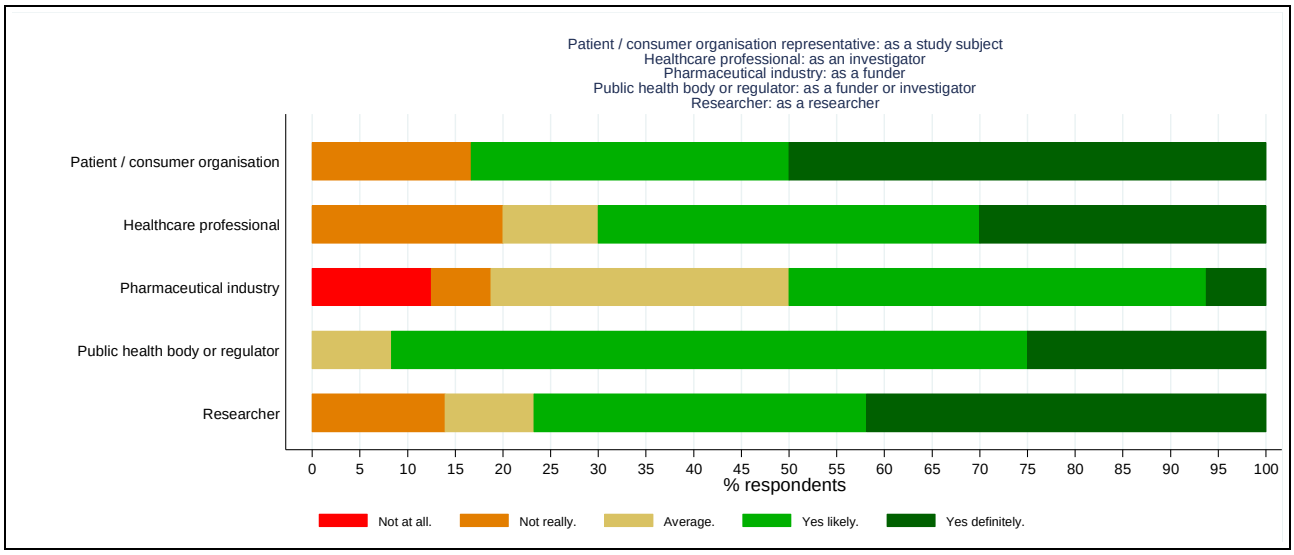

Figure 10: Answers to the five questions investigating whether the respondent felt a higher propensity to participate in a study if compliant with the Code. Each stakeholder category received a different question, as indicated at the top of the figure.

Dimension 5: redundancy

The dimension of redundancy was investigated across all stakeholder categories by asking to choose one statement from a list on the degree of overlap between the Code and other guidelines in the field. The statement chosen more often was '*A useful complementary guideline filling gaps in other guidelines*' (38, 43.7%). The second was '*The Code seems to me overlapping with other guidelines, thus may generate confusion*' (16, 18.4%). Figure 11 shows the answers broken down by stakeholder category. Half of PAT and half of HCP did not rate themselves expert enough on the other guidelines to provide an answer, and the prevalence of this answer was high among REG (5, 41.7%) and RES (11, 25.6%).

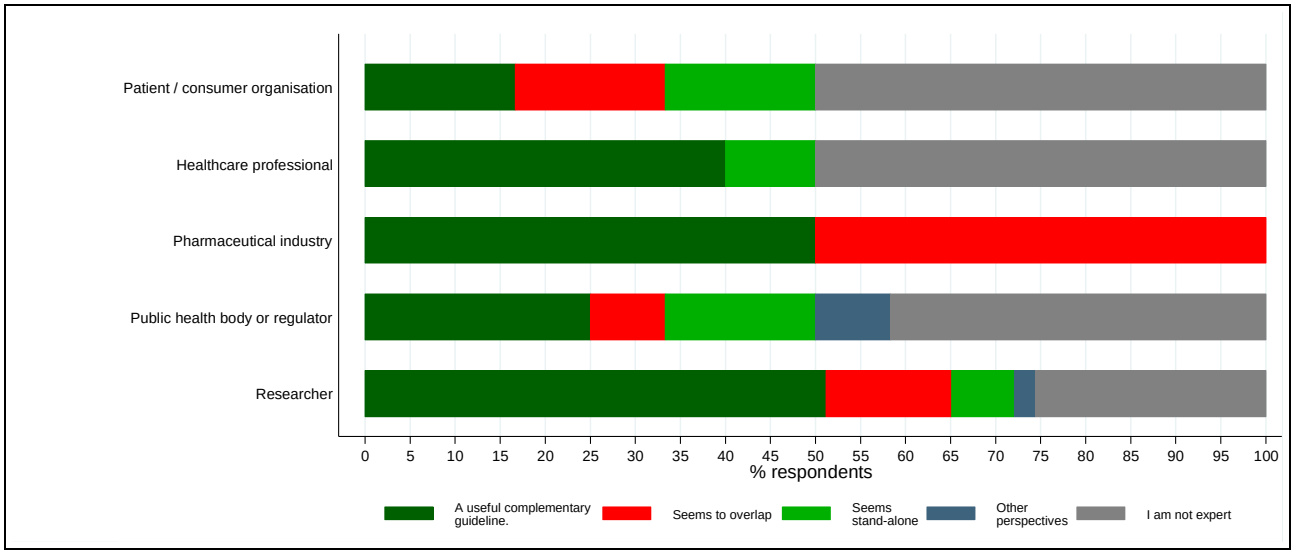

Figure 11: Answers to item #6 '*How do you perceive the Code in context of other guidelines such as ADVANCE, ISPE GPP, ICMJE Recommendations, etc.?*', by stakeholder category.

Summary of comments

Some respondents included comments. In the dimension of usefulness, only one respondent in the PAT and HCP category commented, providing a patient's perspective: that application of the Code would avoid repeating research. Fourteen respondents in the PHARMA, REG and RES categories provided comments, mostly to explain or limit their positive answer. One respondent commented that the questions made the assumption that researchers employed by industry are more biased, and the respondent disagreed. Another, on a similar note, suggested that the initiator is irrelevant with respect to scientific independence. In the dimension of clarity, the only patient commenting suggested that all the persons involved in the study should provide their declaration of interest. In the PHARMA, REG and RES categories, most of the eleven comments reinforced the (positive or negative) answers, but three suggested reasons for difficulties in implementing the Code: the amount of administrative burden, incomplete description of some provisions (i.e. timelines), the impossibility of researchers employed by a pharmaceutical company to take the role of principal lead investigator. One comment suggested that the problem would be addressed by promoting a culture of methods and transparency. In the dimension of trust, the majority of the ten comments specified why and to what extent the provisions increased their trust. A comment by a HCP suggested that trust would be increased if all negative findings were published. One RES respondent suggested that a lack of control of the implementation of the Code's provisions implies that compliance could be declared despite being put in practice. Another RES claimed that studies influenced by the funder may be scientifically valid, and a PHARMA respondent declared that the Code was not correct with researchers from industry, and another that desire for citations/publication was not sufficiently addressed. In the participation dimension, the majority of the five comments specified why and to what extent provisions increased their likelihood of participation, but one RES claimed that researchers in contract research organisations do not need the Code because they respected already other regulations. In the dimension of redundancy, the majority of the ten comments recommended to create a comparison and a unified guidance, and two described limitations or ambiguity of the provisions.

Discussion

The sample of respondents cannot be considered representative of respective stakeholder categories due to the relatively short period of recruitment which was also not systematic. Stakeholders more sensitive to the issues of scientific independence and transparency are likely to be overrepresented. Moreover, the sample is small, especially in the patient category.

Even with this limitation, it is noteworthy that the Code was consistently evaluated across stakeholders as being beneficial for all types of studies, and that the Code is able to increase trust. This indicates that a need to reinforce scientific independence and transparency is perceived across stakeholders, even though we cannot estimate the prevalence of this perception. It was also interesting to observe that understanding of the Code's provisions did not seem to be difficult. More guidance on the interaction between the Code and other guidelines is needed.

The practical problems perceived in implementing and, probably as a consequence, in funding compliant studies from the perspective of pharmaceutical industry may be related to the reluctance to leave control to investigators when the study is a legal obligation in context of a marketing authorisation. However, the Code leaves to the investigators the scientific responsibility, but demands that they inform the funder on possible conditions that hamper the timely conduction of the study. The scientific contribution of researchers employed by industry

is permitted in the latest version of the Code beyond the protocol phase, within pre-specified limits. Dissemination of this aspect is needed to build trust between investigators and pharmaceutical industry, to foster compliance with the Code, with the ultimate aim of improving trust in the evidence generated with pharmacoepidemiology research based on research contracts.

References

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