Comments on draft CIOMS Working Group XI report

Patient Involvement in the development, regulation and safe use of medicines

Posted for comment on 28 February 2022 at:
https://cioms.ch/working-groups/working-group-xi-patient-involvement/
Please return your comments by 11 April 2022 to:
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Reviewers/Affiliations
These comments were developed by members of Global Forum for Research Ethics and Integrity [GFREI] – an open, global, collaborative forum of individuals from 30+ countries focused on research ethics and research integrity. Secretariat support for GFREI was provided by the GE2P2 Global Foundation which hosts GFREI.

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*We agree to our names and affiliations being included in the List of Commentators in the final report: …**YES**….
(No reply to the above question will be interpreted to mean that you have no objection to your details being included)

Notes:

- *Please note that the layout will be improved in the final version, and best efforts will be made to correct remaining typographical and/or grammatical errors, as well those pertaining to references. They are not the focus of this review, but if you happen spot such errors, please include them below.*
- *Permissions are being sought to reproduce some of the illustrative materials in this report. We welcome responses from organisations that own any of these materials and have not yet been contacted in this regard.*
- *Only comments submitted in the table format below will be taken into account. An example is provided below.*

Thank you!

Section	Line no (from)*	Line no (to)*	Concern or text in question	Comment / suggestion for re-wording
Whole document			There are a number of repetitions between the various chapters. For example, consider mentioning the target audience for the document and the reasons why patients should be involved just once. Whilst some of the content is interesting it is not always clear how this relates to the topic of the document. For example, it is unclear how the Belmont report links specifically to the subject of patient involvement.	

* * Or 0 for general comments

Throughout			Patients by definition are vulnerable; they seek medical help, or medical help is sought for them. They are the weaker half of their power relation with those who treat them. Physicians owe them a fiduciary duty--a duty of loyalty and care. They are not necessarily research subjects, nor are research subjects necessarily patients. Research subjects are not necessarily patients. Distinguishing between "Patient" and "patient" clarifies nothing.	Be clear about who is a research subject.

Executive summary	471 And 543, 564 701, 878, 1103, 1549 Etc.	471 And 543 564, 701, 878, 1103, 1549 Etc.	…side effects …	Please replace the word side effects with adverse drug reaction (ADR) throughout the document (as defined in section 5, the word 'side effect' should not be used)
Forward			The discussion of the Belmont Report is very welcome and useful.	Amend only as suggested below.
	321	323	Mention of "principlism" is unnecessary. The term typically has been used to attack the Belmont approach.	Delete mention of "principlism."
	329	329	It is true that "justice" is often used to connote equity (a vague term) and solidarity, but Belmont addresses justice as fairness. Justice as fairness encompasses transactional justice as well as distributional justice.	Change to: Belmont addresses justice as fairness, which encompasses transactional justice and distributional justice.
Forword and throughout	362	369	The word partner is misleading.	Call research subjects research subjects.
Executive summary	471 And 543, 564 701, 878, 1103, 1549 Etc.	471 And 543 564, 701, 878, 1103, 1549 Etc.	…side effects …	Please replace the word side effects with adverse drug reaction (ADR) throughout the document (as defined in section 5, the word 'side effect' should not be used)

1.1 et seq.	651	704	This discussion should be rewritten to eliminate its embodiment of the therapeutic misconception, variously called the therapeutic illusion, that clinical trials and investigational article are likely to be therapeutic. The reason for the research is that the test article has not been demonstrated to be safe and effective for the purpose. Test articles that have been found safe and effective in some applications, are not necessarily safe or effective in others. Test articles that survive Phase 1 studies do not necessarily survive Phase 2. Test articles that survive Phase 2 do not necessarily survive Phase 3. Researchers sometimes confuse matters further by combing Phases 1 and 2 or 2 and 3. These problems are to be found even in studies undertaken with therapeutic intent.	Rewrite this discussion to eliminate wording that conducive to the therapeutic misconception, the therapeutic illusion. Use of the terms "therapy," "investigational therapy," and "therapeutic" to characterize clinical trials and test articles is misleading--especially to prospective and actual research subjects, their caregivers, and health personnel who have not been trained in biomedical and drug research.

Chapter 3	1136	1152	These apply to medicine developers… The guiding principles…	The second sentence of the first paragraph and last paragraph appear to be repeating the same information. Consider stating just once. In fact, I wonder whether it would not be feasible to just mention the target groups of the document once at the beginning of the whole document. The same applies to the reasons why patients should be involved. This could remove some of the repetitions.

Chapter 2 and throughout	1025	1027	Substitution of "participant" for research subject has been promoted by the biomedical and behavioral research industry. It wrongly makes the researchers and the researchees equals, which they are not. The term hides reality. The authors here cite to footnote 36, a training project with heavy sponsorship from industry.	Use accurate language.

Chapter 4, section 4.2	1702	1703	To add three more recommendations as general guidance in considering integrating patients' views into the lifecycle of developing, using and regulating medicines.	Suggestion: to add to recommendations, 1) <u>Strive to safeguard patients' privacy and confidentiality, especially when digital health is involved and patient's data is collected and transferred crossed borders;</u> 2) <u>Ensure that individual patient's preference, including their choice of not engaging, comes first, and not be overridden by patient organization;</u> 3) <u>Ensure that the issue of conflict of interest is given due scrutiny when patient organisations and/or patient experts are involved, as patient representative, in developing, using and regulating new medicines.</u>

Chapter 4, subsection 4.5.8	1944	1944	Though in the recommendation, reference is given to *International Ethical Guidelines for Health-related Research Involving humans (2016)* Guideline 16 and Guideline 17, the crucial part on respecting the preferences of patients is not mentioned in the main paragraph.	Suggestion, to add, [their caregivers.] It is important to whenever possible, seek and respect the wishes and preferences of patients who need special assistance in the informed consent process during clinical research. When patients' preferences are in conflict with their caregiver/legal guardian and/or with their doctors, careful and transparent procedures are required to weigh patients' wishes against the judgement of those involved in their care.
				1)
Chapter 4, section 4.7	1976	2070	The entire section.	This section provides general ideas about types of studies that help to integrate patients preferences and needs into the lifecycle of the development, regulation and use of medicines, thus shall be moves up, after section 4.2 and before section 4.3.
Chapter 4, section 4.4	1816	1821	The entire paragraph.	This paragraph addresses an important issue on 'conflict of interest' and the need for great transparency and governance on the interaction between patient organizations and biopharmaceutical companies. Suggestion: This paragraph should be introduced as general concern and principle in the earlier section 4.2, say, to be inserted between line 1639 and line 1640.
Chapter 4, subsection 4.5.1	1858	1870	Considering learning diversity and that multimedia learning materials have been widely adopted in educational settings, those effective communication strategies and tools should be readily integrated into developing patient engagement materials.	Suggestion: 2) Line, 1858: Use plain language and when appropriate, multimedia materials, to… 3) Line 1862: [educational materials] If needed, developing multimedia communication materials to improve the effectiveness and reach of communication efforts. 4) Line 1865: [educational materials], including non-written, multi-media materials,

Chapter 4, subsection 4.5.5	1909	1918	This sub-section, though emphases 'hard-to-reach' patients, is part of the deliberation on 'diverse and underserved' patients in subsection 4.5.2. Also, in social sciences, the concept 'hard-to-reach' has specific connotation, i.e. minority groups that are stigmatised, felt the need to hide their identities, or those privileged and not open to social inquiries. Thus, given the rarity of occurrences of rare diseases, as individuals and patient groups, their unmet medical need is often neglected, but as patients they are more eager to engage with the science and medical communities than 'hard-to-reach'.	Suggestion: to integrate subsection 4.5.5. with subsection 4.5.2
Chapter 4, subsection 4.5.7	1929	1936	Clinical trial information is part of the information that needs to be communicated to the patients effectively during the lifecycle of developing, using and regulating medicines.	Suggestion: to integrate subsection 4.5.7. with subsection 4.5.1
Chapter 4, subsection 4.5.8	1937	1937	Engaging patients who cannot provide direct input	This subsection discusses context where, under legal constrains, patients would need caregiver/legal guardian to be involved in the informed consent process and sign the form. This is yet a heterogeneous group while many patients are able to provide input into the design and conduct of clinical research. Suggestion: Engaging patients who <u>needs special assistance with informed consent process</u>

Chapter 5	2537			Overall chapter 5 reads more like relating to pharmacovigilance and risk management rather than "use of real-world data" and the particularities on how patient involvement can be meaningful and how it can be achieved. Whilst the section on risk management programs is interesting, it is unclear how this relates to data collection. Of note risk management is also discussed in chapter 2 (Line 1044 onwards) and chapter 8 and this reads differently.
	2566		Data from personal sensors and wearables	Issue on the reliability/ validity of such data should be mentioned, i.e. not all have been sufficiently tested/ validated.
	2591	2622	Introduction to section 5.3	The challenges of patient involvement do not only apply to data collection, but to any involvement of patients. I recommend to move this chapter up to the introduction for the whole document.
	2623	2708		Please consider adding how the involvement of patients in the development of informed consent forms and processes for data ownership can contribute to improved ICF forms and better control of data access.
	2789	2887		The points raised here appear to be more general and not specific to data collection. Consider moving up to the beginning of the document.

	2923			This appears to be a list of "post-marketing" observational studies. Consider explaining how patient involvement in the design etc could be meaningful and how this can be achieved.
	3309			The degree of certainty of a causal relationship is not the only challenge for patients. Understanding the degree of likelihood that a given ADR will happen to them is very difficult to understand because the frequencies provided in the label are based on patient populations. They do not represent a degree of likelihood or an estimate that an ADR will happen to an individual patient.
Chapters 6, 9 and 10				All three chapters are very well written and provide clear examples of how the involvement of patients can be achieved in a successful manner
	3085	3086	In that respect, value-based healthcare becomes '21st-century tendering' for both payers and patients	'21st century tendering' may not be clear to readers. Suggestion: '..value-based healthcare is the tendering process that is likely to work best in the future for both payers and patients.'

10			The case for human subjects research in seriously distressed zones is not self-evident.	Make the case or point clearly to the problem.
10.2	5317	5325	The authors cite Marshall's report for TDR but ignore the report's warnings.	Recognize that there are circumstances in which legal, conscionable human subjects research cannot be done.

Chapter 10, intro	5240	5243		Some LMICs are under conflict and war and this requires a special section.
	5244	5262	The principles for involving patients in low and middle-income countries should be no different 5245 from that in high-economy countries.	The normative SHOULD is too theoretical and not practically feasible.
				Key point 1 and Key point 2 are contradictory. If there are specific challenges in LMICs, then the principles applied need to factor in the challenges.
				Point 4 is theoretically excellent but not practically feasible.
	5277	5290	Box 3 Health challenges in LMICs	These are indeed challenges but instead perhaps the solution is in addressing the causes and not the symptoms and this will solve the problem of patient involvement in general.
	5296	5297	In LMICs, the same guiding principles and goals 5295 apply, but there are also unique challenges and opportunities to take into consideration, 5296 and this chapter focuses on those.	Same comment as above. Specific challenges call for specific review of the peripheral principles and their relationship to the core ones.

10.2	5308	5313	In some LMICs, political fragility – characterised by unstable governance arrangements, civil strife and war – severely disrupts civil structures; people are left without access to a functioning healthcare system. It is impossible to plan and implement sustainable patient engagement activities in these circumstances. In some LMICs, patients may be fearful of voicing opinions that expose failings or weaknesses in the healthcare and governance 5312 structures.	This section needs to be further developed. The ecology of conflict and protracted conflict call for review of principles.
	5314	5319	Absence of ethical standards or ineffective enforcement where they exist, work against patients playing their full part. In medicines research, poor adherence to established ethical principles can mean that patients' views are overlooked, diminished, or misrepresented. In Ethical challenges in study design and informed consent for health research in resource- poor settings, Marshall recommended applying certain principles when obtaining patients' consent; they include:	The sudden move from 5314-5316 to the ethical challenges in informed consent (5317-5323) it too abrupt and while IC is essential, there are other issues that need to be addressed.
10.2.2	5337	5339	In LMCIs professionals often discourage patients from participating in clinical decisions and so reinforce a paternalistic ('doctor-knows-best') attitude	This presupposes that all LMICs are the same and have the same issues which is not the case. This is not the case in all LMCIs. In some LMCIs would be more accurate.
	5347	5348	Leaders and other influential figures in the community are susceptible to manipulation by misleading information and media reports; misinformation can affect how the community responds to requests for collaboration on health or medicine research.	The problem with infodemics and false media reports are present globally and not restricted to LMCIs. This is very well described in Chomsky's Manufactured Consent.
	5349	5353	Communities in LMICs may be suspicious of health interventions and of healthcare providers. In many parts of the world – and not just in RLS – there is mistrust, scepticism, and hostility towards, for example, vaccination programmes.2 Such misgivings lead to the community drawing away from healthcare systems and diminishes the prospects for patient involvement in decision-making.	This is a global problem and not specific to LMCIs and not LMCIs have this suspicion.
	5382	5383	In developed economies, codes of conduct for pharmaceutical companies prevent such 'research'.	In "some" not all.
	5389	5393	Health services are improved by learning from patient experience, but in LMICs, healthcare providers are under considerable strain to attend to these learning opportunities; **treatment is often delivered in ill-equipped facilities and with too few trained health professionals.** The services are unlikely to have the capacity to learn about the benefits of involving patients in policy decisions on the safe and effective use of medicines	This does not apply to all LMCIs
10.2.3	5366	5369	Some of these diseases are 'neglected tropical diseases', so-called because they affect poverty-stricken people in low-income countries; in the past, these mainly parasitic and microbial diseases received little research attention.	Involvement of patients in such areas is a luxury they cannot afford simply because they are fighting to have access to the most basic needs in Maslow's hierarchy.

	5416	5430	Healthcare education and improvement of health literacy can start in schools and be reinforced each time a patient engages with the healthcare system. By understanding patients' beliefs about their treatment and their attitude to healthcare, healthcare providers can resolve misunderstandings and increase trust. Special activities and campaigns aimed at community leaders will promote an understanding of the aims and workings of healthcare systems. For involvement in policymaking, patients should acquire adequate understanding of the disease, research methods and treatments, as well as of regulatory and healthcare systems. This will enable more effective engagement with decision-making in medicine research, development and use. Hand in hand with the education of patients, healthcare providers should be taught to respect patients as equal partners in the management of disease and in healthcare decisions. They should also be taught to seek patients' feedback on treatments and on the use of medicines. A relationship built on trust and respect facilitates patients' involvement in policy decisions	Agreed but the move from the *Ought* to the *Is* is really what matters. Unless there is a plan to do so, not sure how useful this is..
10.3.2.	5437	5441	Sharing success stories of patient participation in mainstream and social media can further empower patients, counter the stigma associated with certain conditions and lead to the formation of active associations as well as umbrella patient organisations that facilitate sharing of knowledge (such as on diseases, treatment, research, regulation, and treatment access) and strategies.	Consent and assent need to be discussed. Not all LMCIs populations have access to social media etc. Literacy levels also play a role.
10.3.3	5472	5475	Researchers and medicine developers should subscribe to the ethical guidelines developed in high-economy countries. The CIOMS publication International Ethical Guidelines for Health-related Research Involving Humans10 covers important issues, including research in low-resource settings. Ethical considerations on patient involvement are discussed in the Foreword and throughout this report.	The core might be the same but periphery is not. So a sifting process is required when adhering to ethical guidelines developed in high-economy countries.
			Three general comments: **1) Not all LMCIs are the same so we cannot generalize.** 2) **These are all important issues but perhaps the best solution is to address the core problem and not its symptoms. With some moral imagination these can be addressed: if we can send satellites to the moon and beyond we can surely relief the plight of the LMCI's and thus allow patients to access their rightful treatment and be involved in the development, regulation and safe use of medicines. This is the only way to actually address the problem and solve it.**	

Appendix 1	6365	6368		Please consider rewording. Pharmacovigilance should not be called 'routine' and the official definition of the WHO is: 'Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem.' (https://www.who.int/teams/regulation-prequalification/pharmacovigilance).

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