TRAINING AND RESOURCES IN RESEARCH ETHICS EVALUATION

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Review of the Draft CIOMS Guidelines Presented for Public Consultation

Position Statement from TRREE – February, 2016

Introduction

This review considers the draft CIOMS guideline update. The update will replace the CIOMS 2002 guideline on biomedical research and the 2009 guideline for Epidemiological Studies. Combining the two guidelines to generate one catch all guideline is the first fundamental change within the new draft. This major change broadens the scope of the guidelines to health-related research with humans. This is a welcome development. However, whether the guidelines remain relevant and instructive across the whole spectrum of health related research is a key consideration of this review.

The purpose and objective of the new guidelines is not set out at this consultation stage, but the assumption is that that the same objectives stand, as were stated in the original guidelines (Purpose Statement of 2002): (i) Guidelines designed to be of use to countries in defining national policies on the ethics of biomedical research involving human, applying ethical standards in local circumstances; (ii) for establishing or improving ethical review mechanisms; (iii) to reflect the conditions and the needs of low-resource countries, and the implications for multinational or transnational research in which they may be partners.

General Comments

a) Document Overview

Reviewers of the draft guidelines are asked to view the document as a whole, rather than just cherry-pick isolated issues. However, contrary to this instruction, the format of the online public consultation only allowed responses to independent guidelines contradicting the logic that the document must be considered as one body of work. However the Working Group on the Revision of the CIOMS Guidelines have been very receptive to general comments via email, and kindly made this available outside of the online consultation. This was announced publicly on the website. Please find the general comments below, followed by a review of specific guidelines.

b) Order of Guidelines

A notable change across the entire document is the order of the guidelines. The biomedical research guidelines of 2002 and epidemiology guidelines of 2009 start with a concentration on the procedure of ethics review, and the informed consent of the individuals, followed by community issues. By contrast, the latest draft provisions start with a focus on how to include less resourced regions in health research and the opportunities for the communities hosting the study projects. This change is seen as positive, but whether this is a change in objectives for the guideline is unclear. A request for further information on what drives this change would be informative to understand the overall aim of the document and the motivations to revise.

c) Breadth of the document

The text of the new guideline is substantially longer than the previous one, to the point where its status as a guideline becomes fragile. The length approaches that of a reference document. For academics, it is a welcome teaching tool. On the other hand for ethics committee members, it is not functional and it is

unclear how it could be used in practice. Moreover, new content is introduced in the clarifications of several guidelines, making the distinction between points of normative import and points of clarification difficult. One example of this risk associated with this vagueness is the treatment of deception in Guideline 10. Moreover, the length of the overall document and density of each issue makes obtaining a comprehensive overview challenging. It is therefore difficult to distill a clear common ethos governing the determination of each individual guideline and commentary. This requires further attention, and editing the draft to a more accessible size would be of help.

d) Scope of the document

The inclusion of epidemiological research is to be commended. It leads however to two issues that, are not adequately addressed.

i) The inclusion of researchers who are not health care providers is now implied. This should be explicitly stated. Since the guidelines are about ethical principles, we support the idea that their scope should not be limited to health care providers. In terms of protecting research participants, it does not make much ethical difference whether the researcher is a physician, a nurse or a social scientist. This inclusion of non-health care providers among the population to whom the revised guidelines apply needs to be clearly identified and stated in the new text.

ii) The limits of what constitutes research under the new guidelines are not clear. For example, Guideline 10 now states that “When a prospective study is performed under a public health mandate or by public health authorities such as disease surveillance, normally neither ethical review nor a waiver of consent is needed because the activity is mandated by law”. This could read that such activity never requires ethical review; or that it sometimes does, but provides no guidance on the circumstances where ethic reviews is necessary. It could also be read to imply that when an activity is mandated by law, it does not require ethics review. This certainly could not apply, of course, to clinical trials required by drug regulatory authorities.

e) Research Ethics and Human Rights

The new draft update attempts to confront an ever expanding catalogue of practical challenges that face international health research projects, and this is commendable. However, the guidelines do not adequately foster the relationship between research ethics and human rights - Be it respect for dignity through adequate safe guarding of confidentiality; the realization of the right to health through creating access to health and ancillary care; reducing health inequalities through better requirements of research prioritsation; respecting individual autonomy and community sovereignty through protection of the vulnerable and effective community engagement; protecting against discrimination and promoting equity through providing strong mechanisms of collaboration and capacity building. Greater consideration of the Universal Declaration on Bioethics and Human Rights 2005 along with a thorough human rights impact assessment of the suggested guidelines would focus the recommendations. In addition this would bring a framework of consistency and unity to the document, which at the moment is hard to ascertain.

f) Language

The consultation is conducted predominantly in English, and comments in other languages are only accepted in Spanish. This limits the capacities of many stakeholders - researchers, NGO, patients' organization from many countries in the world, especially those from French speaking sub-Saharan Africa, etc. In view of the original objectives of the CIOMS Guidelines to address the needs of low resources countries, this seems a questionable strategy.

Guideline Review

A few guidelines deserve special attention because they have been deleted or added from the existing documents. Below is a selection of guidelines. Guidelines that are not referred to may also need further specialist attention but have not been chosen for this specific review, even though they may also require further revision. This is the TRREE contribution to the public consultation.

Deletions

Guideline deletion (previously 18): Safeguarding Confidentiality

> Before turning to the new additions in the provisions, there is one notable deletion to mention. There is no longer a standalone provision on safeguarding confidentiality (guideline 18 in both the CIOMS 2002 and 2009 guidelines). This warrants a further remark on the limited format of the online public consultation. By inviting review of only the presented draft guidelines, there is no space to challenge deleted provisions. **This is a clear oversight which brings the transparency and democracy of the public consultation process into question.**
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> The decision to delete guideline 18, "Safeguarding Confidentiality" is arguably an overly bold decision, especially at a time when information is generated across ever expanding numbers of multi centre studies; stored simultaneously in several locations and formats; replicated and

transported at speed, and; the use of data and diagnostics are continuously changing. Instead now the issue of confidentiality is raised as one consideration within a number of other guidelines. In effect the requirement has been absorbed into the document. Confidentiality is now a feature of guideline 4 (potential benefits and risks of research), 11 (Use of Stored Biological Materials and Related Data), 12 (Use of Health-related Data in Research), 18 (Woman as Research Participants) and 22 (Use of Online Information or Tools in Health Related Research).

It is recognised that the deletion of the previous guideline on Safeguarding Confidentiality can be understood as a way to avoid repetition of content otherwise included elsewhere. However, this change represents a decrease in the salience of confidentiality. This is to be regretted, especially during a time where risks associated with confidentiality have remained important, and have become more difficult to protect. Guidelines 11 and 12 address the use of stored biological materials and related data, and the use of health-related data in research. Most research ethics guidelines are currently predicated on the possibility of anonymisation. This possibility is becoming increasingly illusory as the possibility of cross-matching large datasets improves. It is accepted that the revised guidelines recognize this, and this is a commendable point. They fail, however, to provide robust recommendations to protect confidentiality in such a context. The more difficult it becomes to anonymize data, for example, the more important it becomes to retain the ability to remove personal data from a dataset. This point should be clearer.

The sufficiency of the draft guidance on safeguarding confidentially is in question following the suggested deletion. Now as a subsidiary of other relevant research issues, it is generally stated that the confidentiality be adequately “safeguarded” and “guaranteed”. There is limited discussion on the circumstances that can lead to breaches of confidentiality, or methods to insure that there are “adequate” provisions to safeguard confidentiality. The decision to remove a confidentiality guideline from the draft is hard to comprehend, when it remains a key feature of the updated Declaration of Helsinki, 2013 (DoH provision 24). Even more so, given that the original purpose of the CIOMS guidelines is to clarify instructions on how the ethical principles of DoH could be practically applied in developing countries. Further still, at present, the World Medical Association (WMA) is in the final stage of adopting a Declaration on Health Databases and Biobanks. The decision of CIOMS to remove a confidentiality guideline raises additional concerns. This is especially true in regions, where data protection laws may not have kept pace with scientific endeavor, and the ever changing nature of confidentiality protections. At the very least within each relevant section the guidelines should state what questions need to be asked of a research project to ensure the correct measures are put in place for adequate and appropriate confidentiality protection. These questions are not currently stated. It is suggested that an appendices for the guidance could be a table detailing different types of data, the confidentiality challenges, and possible protective safeguards.

Specific comments

Guideline 1: Social Value

The term “social value”, nobly features for the first time in these guidelines, taking the place of the old requirement of “Ethical Justification and Scientific Validity of Biomedical Research Involving Human Beings.” This is an exceptionally important addition, and is a commendable change in the guidelines. The ethical principle of social value strikes the necessary balance between scientific advancement, equitably responding to human conditions and realizing the human right to health. With the introduction of the principle the guideline bridges the gap between conducting commendable science and making a contribution to the health of the populations where health research is being carried out, a necessary component in human participant research. The concept of social value is the ethical justification for research into health.

The idea that health research must be a social good first appeared in The Nuremberg Code at article 2 which states: “The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.” Furthermore, the consideration of social value is heightened when international collaborations are conducting health research in resource limited settings. This has also been recognized in subsequent guidelines, notably UNAIDS guidelines and MSF Research Ethics Frameworks. It is now warmly welcomed, that the principle of social value is also included in the CIOMS guidelines.

The commentary on this guideline does instruct that there is “respect and concern for the rights and welfare of individual participants and the communities in which research is carried out”, but does not specifically mention realizing the right to health as a necessary component of health research. This objective should be clarified and endorsed within the guidelines. Further strengthening this link will foster the relationship between health research and development, as recommended in the World Health Report of 2013: Research for Universal Health Coverage.

Guideline 2: Responsiveness

Guideline 2 states that researchers and sponsors must “Make every effort in cooperation with government and civil society to make available as soon as possible any intervention or product developed, and/or knowledge generated, for the population or community in which the research is carried out. This requirement does not preclude capacity building or the provision of additional benefits to the population or community.” This wording is an improvement over the previous guideline, but it is still too weak. Research participants in low-resource settings should get a fair deal, and this may include availability of interventions or products developed by the research, and/or other benefits. The current wording, however, does not mandate that the overall deal must be fair.

In particular within resource limited settings, prior agreement of reasonable availability for post-trial products is unlikely to adequately fulfill the requirement of responsiveness in most research projects. This is especially true, where the health research is not biomedical in nature, or at an advanced stage of a phase III trial. A greater duty of responsiveness should be placed on stakeholders to agree healthcare provisions for participants through the study, system strengthening requirements and managing the end of a study programme. The provision of responsiveness should safeguard against individual, community and resource exploitation and provide a mechanism to achieve mutual gain from research ventures.

Guideline 3: Distribution of benefits and vulnerability

The guideline repeats the necessity to justify the exclusion of groups in need of special protection, in order to equitably distribute burdens and benefits. However, experience has proven that justifying the exclusion of groups in need of special protection is rather simple. Whenever the vulnerable population has higher risks of health harms, of adverse effects, drug-interaction, or any clinical condition that might have an impact on the effect of the experimental drug, two arguments can be out forward. The first one would be the necessity of protecting those vulnerable persons from health-related harms of the research because they have higher chances of suffering from them and therefore need to be excluded. The second argument is that it could weaken data reliability. In fact, unless a sufficient number of vulnerable persons having the exact same clinical condition are recruited to create a sub-group of subjects, their participation in the trial would be detrimental to the homogeneity of the results. As a result, it seems easy to exclude vulnerable persons, which is however counterproductive when their vulnerability concerns their health condition. The more they are excluded from clinical trials, the less the marketed drugs will be adapted to them. Instead of being protected, they get marginalized and suffer from inadequate access to treatments. As a consequence, in order to actually respect a fair distribution of benefits in research, the requirement should be not only to justify the exclusion of persons in need of special protection, but provide incentives to support their careful inclusion.

As the comments rightly observes: “equity may require special efforts to include members of those populations in research”, but at this point it seems like they are only referring to guidelines 17, 18 and 19, respectively children and adolescents, women, and pregnant women”. However, there are a lot more vulnerable persons who need to be included in biomedical research as much as children, women and pregnant women. It should be very clear that those three categories are only examples. For instance, it seems surprising that elderly people are not also mentioned as an example of a previously under-represented group of persons. Considering the increase of age-related conditions such as frailty or dementia, frail or demented older persons should be considered as urgently needing to be systematically included in biomedical research, especially as they represent a growing part of the population in Europe.

Guideline 4: Risk assessment

The approach to risk assessment proposed in Guideline 4 is much more robust than in previous wordings, and although it may turn out to be difficult to implement it has the advantage of requiring that all risks be systematically taken into account.

Guideline 5: *Placebo use*

Guideline 5 integrates the usual provision that "The use of placebo is uncontroversial in the absence of an established effective intervention." After the controversy surrounding the Ebola treatment trials in the summer of 2015, this statement is no longer substantiated. In situations where a promising intervention is tested to treat a highly lethal disease for which no effective treatment exists, controversy does exist. Not integrating recommendations for such cases would be an important missed opportunity.

Guideline 7: Community Engagement

For the first time a duty of community engagement is defined in the CIOMS new draft guidelines, recommending that "Institutions should engage potential participants and communities in a meaningful participatory process..." The normative purpose of requiring prior engagement needs to be better explained in the draft guideline. It is not merely a process of 'knocking before entering a room', but rather an act of inclusion, partnership and due respect for host communities. Ultimately community engagement and inclusion is required to enhance the protection of research participants and community health. This is implied with the Cambodia case study provided in the commentary but not explicitly stated in the current draft guideline, as it should be. Guideline 7 should require that community engagement be comprehensive and transparent. This includes that funding mechanisms, for all the foreseeable costs of research, including the end of research are identified amongst stakeholders prior to the undertaking of a study.

Certainly community engagement model assists in ensuring a fair distribution of benefits amongst stakeholders. However, there are also challenges, especially in respect of relational ethics. For example concern of undue influence and the equality in collaborative negotiations. This weakness is recognised in the draft guidelines, but it incorrectly recommends that informed consent will remedy this exploitative pressure. Additional protective measures are necessary to truly preserve individual and community voluntariness, and defend against corruption. It is the strength of guidance that assists to safeguard against these limitations and facilitate balanced and effective dialogue between stakeholders. The guidance needs to focus, not only on the presence of engagement, but also on how community engagement operates. Engagement must be responsive to different features of community – local services, politics, finances, traditions and customs. Community Engagement in itself does not make research ethical, this is dependent on the manner in which the process is carried out; and the draft guidelines ought to stress this point.

Guideline 8: Collaborative Partnership and Capacity Building for Research and Review

Guideline 8 is an expansion of the previous CIOMS guideline number 20 labelled "Strengthening Capacity for Ethical and Scientific Review and Biomedical Research". The new guideline has radically changed position in the document; moving from position number 20 to number 8. If all the guidelines are required to be equally considered then possibly this position change is of no relevance. However the move up the ladder of extensive guidelines may also be indicative that it requires prioritisation or is at least suggesting collaboration and in terms of "timing" capacity building needs to be considered early on in health research. Early discussion of capacity building in collaborations should be stated explicitly. Moreover capacity strengthening is no longer stated as "an ethical obligation" but a "must": "Researchers and sponsors who plan to conduct research in these communities *must* contribute to capacity building for research and review". The use of language indicates the stringent requirement of capacity strengthening, regardless of differing ethical viewpoints. This is a warmly welcomed change.

The recommendation states that "It is the responsibility of governmental authorities in charge of health-related research involving human participants to ensure that such research is reviewed ethically and scientifically by competent and independent research ethics committees and is conducted by competent research teams." Two important aspects have been missed out of the wording.

i. Some provision should be made to ensure that there is oversight even in the countries where governments lack the capacity or the will to endorse this responsibility. For example, governmental authorities in the countries where sponsors are located, or where applications are made to for authorization of drug and device sales, could have responsibilities to verify that research was conducted in accordance with the content of this guideline. Guideline 23 almost reaches this point but stops short of recommending an international mechanism to verify the quality of ethics review.

ii. Some research ethics committees are competent but lack authority. Ideally, some provision should be made to ensure that such committees obtain greater recognition. In any case, communication between research ethics committees in case of multi-center research should be required, and mechanisms designed to facilitate such communication should be encouraged. This is now a part of Guideline 23. It should also be an explicit possibility, however, that problems identified in one country should lead to another ethics committee recommending halting the trial.

Under the guideline commentary, the named activities of capacity-building have expanded from five activities to six. The new additional activity being the requirement that there are "arrangements for joint publication consistent with recognized authorship requirements and data sharing." This reflects an ongoing imbalance between science, medical publications and use

of data between high income and low income countries. However the dependence of the guideline on “recognised authorship requirements”, does not tackle the complicated issue of authorship faced by large multinational research trials, across stakeholders from differing resource regions. A push for equitable opportunity in authorship and publication would be a recommended approach. This is also important to uphold international instruments supportive of rights and freedoms, such as implementing practices free from discrimination.

The guidelines continue to require that strengthening research capacity is through “dialogue and negotiation”. This method in itself does not ensure collaboration is fair and equitable. This is particularly true in the circumstances where partners are not in a position to contribute equal finances to a project, which is often the case for health research of resource limited regions. To safeguard against power indifferences more innovative forms of collaboration should be considered. For example the requirement could be to complete the following three tasks at the formation of a collaboration and ahead of the research activity i) local research agenda setting with ii) capacity needs and priorities assessment amongst partners of international health research, and iii) create a Memorandum of Understanding (MoU). Ensuring these basic steps are minimal requirements for creating an environment of inclusion, development mutual learning and social justice. Negotiation, especially demand-led negotiation, does not create cooperative collaboration.

Guideline 11: Use of stored biological materials and related data

World Medical Association (WMA) is presently working on a Declaration on Health Database and Biobank to complement the Declaration of Helsinki, it is important that the CIOMS guidelines coordinate and are congruent with this new Declaration.

The CIOMS guideline refers to the broad term of biobank, without making a clear distinction from a related but separate concept of a biorepository. The two systems are different and the handling of the samples changes when used for a specific research (bio repository) or within several studies not initially defined at the outset of a research project (biobank). The period of storage of human biological material in Biorepository should be in accordance to the timeline of the research. The definitions set out below are just one example used by the National Health Council of Brazil under Resolution 441/11. It is recommended that similar definitions are set out for the CIOMS guidelines:

"Biobank”: organized collection of human biological materials and associated information collected and stored for research purposes, in Accordance with pre-defined technical, ethical and operational regulations or standards, under the institutional responsibility and management, without commercial purposes;

"Biorepository": collection of human biological material, collected and stored During the execution of a specific research project, in Accordance with pre-defined technical, ethical and operational regulations or standards, under the institutional responsibility and management, without commercial purposes "

In the handling of biological samples, it is very important to consider the case of research involving more than one institution, there must be an agreement between the participating institutions, contemplating ways of operation, sharing and use of human biological materials stored in Biobank or Biorepository. This must further include the possibility of future dissolution of the partnership and the consequent sharing and allocation of data and materials stored, and should a provision of Informed Consent.

One further point is with reference to patents and commercial use of human biological materials stored in Biobanks and Biorepositories. Different laws apply in different jurisdictions and this needs to be respected. In particular careful adherence needs to be considered in multi-centre studies, and should not undermine the development opportunity or health of resource limited populations.

The terms of withdrawing consent under guideline 11, need to be detailed with greater attention. The suggested wording may read as follows:

"the research subject or her/his legal representative at any time and without any charges or losses, should have the possibility to withdraw her/his consent for care and use of biological material stored in a Biobank or Biorepository. The withdrawal of consent should be formalized by written documentation signed by the research subject or her/his legal representative, and her/his samples should be either destroyed or returned to him. Ffuture use of the data and biological materials are not permitted after the consent's withdrawal."

Guidelines 11 and 12: Unsolicited findings

Guidelines 11 and 12 address the possibility of unsolicited findings, but do so incompletely. In addition to the aspects addressed in this guideline, the possibility of unsolicited findings can generate expectations that a clinical diagnosis process is integrated in to research projects, even when this is not the case. Participants may then expect that researchers will 'see everything' about their health and be falsely reassured by the absence of unsolicited findings. In the research setting, it is important to clarify that a diagnostic process is not the aim, and that in many instances clinically relevant information will not be identified. Any possibility of therapeutic misconceptions must be addressed and clarified directly in research proposals and consent forms.

As a further addition to guidelines 11 and 12, it is also necessary to clarify the type and quantity of materials shared and determine their destination after use. For example the commentary

needs to define the responsibility for the ***destruction of collected biological samples or data in the circumstances where samples are not-used*** or where their use has finished. Patients need to be informed of what are the conditions under which their samples and data would be destroyed, and furthermore that they have the option to destroy their data at any time. In particular since WMA is working on a Declaration on Health Database and Biobank to complement the Declaration of Helsinki, it would be important that the CIOMS guidelines be coordinated and congruent with this new Declaration.

Guideline 13: Compensation

Guideline 13 requires that "Research ethics committees must evaluate monetary and other forms of compensation in light of the traditions and socio-economic context of the particular culture and population in which they are offered". Ethics committee members are often drawn from the more privileged strata of their own society, and inequality within their society may make the situation of some difficult to envisage for others. It would be useful to add "Consultation with the local community may help to ascertain this even in the case of research conducted in the researchers' own community."

Guideline 15: Vulnerability

An important aspect of the account of vulnerability in the revised guideline is that the "increased likelihood of being wronged or of incurring additional harm" does not only center on consent-related wrongs and harms. Persons who are placed at greater risk of physical, psychological, physiological harm than others, for example, will require special protection through targeted assessment of their specific risks and measures to mitigate against harms. This is for instance the case of children, pregnant women or of most elderly people when they are frail, or have comorbidities. Safeguards for those vulnerable persons have to target a specific benefice/risk evaluation taking into account their clinical condition.

Moreover persons who are at greater risk that their confidentiality will be breached are another example of a vulnerable group. In these cases, allowing no more than minimal risk for procedures or relying on the permission of legal guardians will not constitute appropriate protections.

The new suggestion of avoiding the labelling approach of vulnerability is welcomed. However, we suggest this approach be taken further. The current comment describes "characteristics" which make it likely for the person to be vulnerable. Such an approach does not distinguish itself enough from the labelling approach. The first steps to recognize vulnerability would be to identify potential harms that are specifically related to clinical trials, and from there, identify vulnerable participants. The potential harms of clinical trials could be:

i. Consent related harms

ii. Health related harms

iii.Confidentiality related harms

This is especially important as some persons are only particularly vulnerable to one of the harms (for example, a pregnant woman, or a frail, but not cognitively impaired, elderly persons may not care about personal data being published), some participants are vulnerable to two of the harms (children are particularly vulnerable to both health-related harms and consent related harms), and some are vulnerable for all three. Yet it is crucial to distinguish the harms in order to identify the adequate protection (legal guardian, low risk or data protection).

It is also very surprising, according to the current circumstances and the ageing of the population, that the mention of the vulnerability of elderly people has been deleted from the comments of the guideline on vulnerability. Even in the attempt to stop the labelling approach of vulnerability, and to stop the stigmatisation of elderly people, the vulnerability of a lot of older adults has to be highlighted, especially the proportion of elderly people is increasing, and within that population physical frailty and dementia are clinical conditions that are constantly expanding.

Guideline 16: Advance Directives

Advance directives for emergency research with incompetent adults are introduced in guideline 16: "the researcher and the research ethics committee must ensure that (…) in the case of emergency research, participants have made advance directives, where feasible, for participation in research while fully capable of giving informed consent or their communities have been engaged". It seems unfortunate that the comments don't give further details on how this option should be considered, or when is it ethically acceptable.

For instance, it should be clearer that the advance directive has to have been specifically written for that particular trial, and that all requirements validating an informed consent have been fulfilled. This is especially important to clearly state, as the advance directive seems to be the sole safeguard of the patient's right at that point (no proxy).

The conditions under which the advance directive is still valid when there is a change in the patient's condition, in the protocol of the trial, or in the balance benefice-risk should also be clarified.

It should also be clarified whether the advance directive of the patient (written at the time where he was legally capable) overrules the objection or refusal of the currently incapable patient? Has the incapacitated adult the right to change his mind in comparison to when he was legally capable? As the recommendation is currently formulated, it seems like the patient would be bound by his advance directive.

Finally, the introduction of advance directives for research, even for now limited to emergency research, might open the discussion for the validity of advance directives in normal (not emergency) biomedical research. It would be necessary to mention that option, and whether it would be acceptable or not, and under which conditions. In fact, with the growing proportion of

Alzheimer's disease and related dementia, and the urgent need of more research in that field, advance directives could be a precious tool to use. However, ethical guidance for such use is needed. Researchers and ethics committees are facing this challenge more and more often, and it would again, be a missed opportunity to ignore that growing phenomenon.

Guidelines 16 and 17: Incompetent refusal

Guidelines 16 and 17 accept circumstances –described as exceptional- where research participation is considered the best available medical alternative for individuals who are incapable of giving consent. In such cases, a potential participant's refusal does not have to be respected. It is not clear how this assessment will be made and kept clear of the risk of conflicts of interests or of the therapeutic misconception. Furthermore, there is no information how such a decision should be implemented, and specifically the degree of constraint that might be judged acceptable, also lacks clarity.

Guideline 19: Pregnant women

The revised CIOMS guidelines should be commended for allowing continued participation in research for women who become pregnant during their participation. Regarding the possibility of participation in research directed at the health of the fetus in Guideline 19, however, it seems insufficient to make the pregnant woman the sole decision-maker. She should of course never be compelled by anyone to participate in such research against her will. Whether she should be able to consent alone, however, is more questionable. It could be more prudent to require consent by both prospective parents, when they are known, for the inclusion in research directed solely at the health of the fetus. When even part of the research is directed at the health of the pregnant woman herself, she should remain the decision-maker.

Guideline 20: Research in Disaster situation

In the guideline commentary, it is clearly stated that "*the first and foremost obligation in disaster situation is to respond to the needs of those affected*", and there is a call for making sure the researchers do not "*unduly compromise*" the humanitarian action. Due to the exceptional circumstances in disasters for the affected population, the level of despair and of level of basic needs to be covered, the potential risk of conflict of priorities between aid and research must not be tolerated. The guideline very correctly mentions that research in such circumstances can not be conducted if it could otherwise be undertaken in a non-disaster situation. Equally, research will not be carried out if a proper aid response is not first offered to the affected population (imposition of conditionality). Research protocols and ethical committees must ensure that any population involved in research must have their basic needs (in terms of health, food, water, shelter) covered by the response teams or included in the research project. (Special emphasis on Guideline 6)

In the situation of a disaster, the response staffs delivering assistance are often overwhelmed by their tasks. As Guideline 20 clearly states, "research must not unduly compromise the disaster

response". The guideline does not however go far enough and explicitly state that where research is conducted, then this burden of activity needs to be fully compensated. Where skills or materials from the disaster response are relied upon for a research purpose, then this must be sufficiently compensated. This could mean for example the addition of extra materials, human personnel or finances, so that the delivery of care is not jeopardized by the research itself. This requirement needs to be stated clearly as a new provision under guideline 13 and/or as a specific mention in guideline 20

An extra criterion that needs to be mentioned and emphasised in a disaster situation, is respect for security. Research teams are responsible of their own security mechanisms. Should they work in collaboration with response teams providing aid to the affected communities, research projects must abide to the security rules and procedures established by the response teams because those rules and mechanisms are developed to allow secured delivery of assistance.

The disruptive nature of any disaster imposes a greater duty of care when conducting the informed consent procedures (guidelines 9 and 15) with the traditional protection mechanisms of the individuals and communities (family links, disruption of the public services or mechanisms), The level of dependency of affected population has an impact on its capacity to exercise its freedom of choice. To complement or compensate the normal procedure, an extra (light and efficient) visa mechanism should be developed with the local branch of the WHO delegation ensuring the respect of public good.

In case of biological material collection (Guideline 11), the informed consent must be obtained on the use of the sample while the samples still belong to the individuals or by delegation to the community, as the circumstances dictate

Guideline 24: Public Accountability for Health-Related Research

As a newly added Guideline, the first question is does this add a protective measure that is not otherwise covered in the guidelines, in this case, the answer seems to be no. The guideline is entitled Public Accountability and focuses on the registration and responsible sharing of trial data, on which the public can confidently rely. This is very closely related to guideline number 1 (social value): "The social value of research is ultimately grounded in the quality of the information … and its contribution to … public health." Data integrity is clearly a component of quality data and the ability to adequately drive improvements in public health. Creating an additional term of "public accountability" seems to add no further protection to participants or communities involved with research, and adds confusion to the concept of social value. As it stands "Public-Accountability", is too wide to give meaningful ethical direction. Perhaps a more appropriate title would be "Data Sharing, Result Publication and Authorship Rights." These related activities encounter various ethical challenges in practice and especially in the context of resource limited regions. However most of these ethical issues are discussed with in various

other guidelines, namely guideline 3 (Equitable distribution of benefits and burdens in the selection of groups of participants in research); number 4 (Potential benefits and risks of research); number 7(Community Engagement) and; number 8 (Collaborative partnership and capacity building for research and review). If there are further issues that are not raised in any other guideline, or if it would be better to group existing provisions together then this would justify the newly defined guideline. An alternative approach would be to extend or develop existing guidelines. At present the new provision contributes little to protect against harm or adequately direct research teams.

Guideline 25: Conflicts of interests

Guideline 25 provides for the disclosure of conflicts of interests. This disclosure, however, should also include disclosure of strategies to manage and mitigate these conflicts. Simple disclosure is not sufficient to assess when conflicts of interests are problematic and when they are not.

Concluding Remarks

The CIOMS revision committee have undertaken an exceptionally challenging task, and demonstrated remarkable craftsmanship and dedication to the process. The bringing together of two established sets of guidelines to produce one new updated guideline, capable of instructing numerous fields of health research activity, is an ambitious exercise, and; we strongly support this approach. Substantial improvements have been made with the publication of this draft guideline, and the revised document makes a strong case for the need to change. Now close attention needs to be given to the draft provisions to establish whether they successfully achieve the aims of the document. We hope the comments of TRREE will contribute and helpfully shape the provisions set out in this exceptionally important health research guidance.