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PERSPECTIVE

Waivers of informed consent in research with competent participants and the Declaration of Helsinki

Rafael Dal-Ré[1]

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The World Medical Association started revisions to the Declaration of Helsinki in 2022 and it will have to address numerous issues that have arisen in research ethics since the last 2013 revision [1]. In the face of critical issues that have surfaced during the COVID-19 pandemic, less salient but nevertheless critically important issues may go unnoticed. One of these concerns is the conditions under which it is ethically permissible to modify or waive written informed consent in research with competent participants.

The Declaration of Helsinki recognizes that there are circumstances in which it is permissible for individuals who do not themselves provide informed consent to participate in research. In research with persons who are incapable giving informed consent (e.g., children, dementia patients), investigators must seek written informed consent from the legally authorized representatives. In trials conducted with individuals that are incompetent for a limited period of time (e.g., hospitalized COVID-19 intubated patients) a deferred consent must be sought: when legal representative is available, their written consent must be followed by the participant's written consent to remain in the trial once he/she can provide it. However, the Declaration of Helsinki, currently recognizes no exception to the requirement that competent individuals must provide informed consent to participate in medical research [1]. As a result, the guidance in the Declaration of Helsinki diverges from the Council for International Organizations of Medical Sciences (CIOMS) guidelines [2] −prepared in collaboration with the World Health Organization and is the ethics code commonly followed in low- and middle-income countries−, that allow for the modification and waiver of written informed consent if the research fulfills three conditions: a) it would not be feasible or practicable without the modification or waiver of informed consent; b) has important social value; and c) poses no more than minimal risk to participants. For research involving humans, the regulations of Australia [3], Canada [4], and the USA [5] ask for the fulfillment of several requirements, the two critical ones are the impracticability of the research and that it does not involve more than minimal risk (Table 1). The research must always be approved by the relevant research ethics committee [2–5].

Provisions for a waiver of informed consent are common in certain types of research. Thus, for example, depending on the unit of randomization, randomized controlled trials (RCTs) can randomize individuals or clusters (groups) of persons. While the former is the classical RCT useful to evaluate almost all type of interventions, the latter are increasingly common beyond the typical RCTs assessing health promotion and educational interventions. The possibility of conducting ethically-sound cluster RCTs with a waiver or alteration of written consent is well established: the interventions and data collection should pose no more than minimal risk and the research will be unfeasible without a waiver or alteration of informed consent [6]; conversely, a similar approach for certain types of individual-level RCTs is less accepted [7] −although both types of trials share the same ethical requirements. Thus, for example, the EU regulation on clinical trials with drugs accepts a modified ('simplified') consent for low-risk cluster RCTs but not for low-risk trials randomizing individuals [8]; the same approach is proposed for legislative changes for clinical trials with medicines and medical devices in the UK [9].

Certain type of participant-level comparative effectiveness RCTs in competent individuals can be facilitated by

✉ Rafael Dal-Ré
rafael.dalre@quironsalud.es

[1] Health Research Institute-Fundación Jiménez Díaz University Hospital, Universidad Autónoma de Madrid, Avda Reyes Católicos 2, 28040 Madrid, Spain

Table 1 Modifications and waivers of informed consent in Australia, Canada, and USA regulations and in CIOMS guidelines[a]

Australia [3]	*Canada* [4]	*USA* [5]	*CIOMS (WHO) guidelines* [2]
2.3.9.- Only an HREC[b] may grant waiver of consent for research using personal information in medical research, or personal health information. (…) 2.3.10.-Before deciding to waive the requirement for consent (…), an HREC (…) must be satisfied that: a. involvement in the research carries no more than low risk[c] to participants b. the benefits from the research justify any risks of harm associated with not seeking consent c. it is impracticable[d] to obtain consent d. there is no known or likely reason for thinking that participants would not have consented if they had been asked e.there is sufficient protection of their privacy f.there is an adequate plan to protect the confidentiality of data g. in case the results have significance for the participants' welfare there is, where practicable, a plan for making information arising from the research available to them (…) h. the possibility of commercial exploitation of derivatives of the data or tissue will not deprive the participants of any financial benefits to which they would be entitled i. the waiver is not prohibited by state, federal, or international law	Article 3.7A.- The REB[b] may approve research that involves an alteration to the requirements for consent set out in (…) if the REB is satisfied, and documents, that all of the following apply: a. the research involves no more than minimal risk[e] to the participants; b. the alteration to consent requirements is unlikely to adversely affect the welfare of participants; c. it is impossible or impracticable[f] to carry out the research and to address the research question properly, given the research design, if the prior consent of participants is required; d. in the case of a proposed alteration, the precise nature and extent of any proposed alteration is defined; and e. the plan to provide a debriefing (if any) that may also offer participants the possibility of refusing consent and/or withdrawing data and/or human biological materials, shall be in accordance with (…)	45CFR 46.116.f.3.- In order for an IRB[b] to waive or alter consent as described in this subsection, the IRB must find and document that i. The research involves no more than minimal risk[g] to the subjects; ii. The research could not practicably be carried out without the requested waiver or alteration; iii. If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format; iv. The waiver or alteration will not adversely affect the rights and welfare of the subjects; and v. Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation	Guideline 10.- (…) A REC may approve a modification or waiver of informed consent to research if: 1. the research would not be feasible or practicable to carry out without the waiver or modification; 2. the research has important social value; and 3. the research poses no more than minimal risks[h] to participants

HREC human research ethics committee, *IRB* institutional review board, *REB* research ethics board, *REC* research ethics committee

[a]CIOMS guidelines were prepared in collaboration with the World Health Organization, Geneva, Switzerland

[b]Names received by research ethics committees in different jurisdictions

[c]Research is 'low risk' where the only foreseeable risk is one of discomfort. Where the risk, even if unlikely, is more serious than discomfort, the research is not low risk. Research is 'negligible risk' where there is no foreseeable risk of harm or discomfort; and any foreseeable risk is no more than inconvenience. Where the risk, even if unlikely, is more than inconvenience, the research is not negligible risk[3]

[d]For example, due to the quantity, age or accessibility of records[3]

[e]Minimal risk: Research in which the probability and magnitude of possible harms implied by participation in the research are no greater than those encountered by participants in those aspects of their everyday life that relate to the research[4]

[f]Incapable of being put into practice due to a degree of hardship or onerousness that jeopardizes the conduct of the research; it does not mean mere inconvenience[4]

[g]Minimal risk (45CFR 46.102.j): the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests

[h]Minimal risk standard: is often defined by comparing the probability and magnitude of anticipated harms with the probability and magnitude of harms ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests[2]

waiving or altering written consent: low-risk pragmatic RCTs (or low-intervention RCTs in the EU regulation terminology [8]) for the assessment of commercially available medicines withing the approved labels (or evidence-based), with no more risks or burdens to participants than in usual clinical practice [7]. Since randomization in these trials poses no or minimal additional risk to participants compared to usual care, the key element to consider by investigators and research ethics committees (RECs) is whether the 'impracticability' requirement is met. Although the meaning given to 'impracticability' has been diverse between researchers and RECs [10], there are regulations that make its meaning explicit (Table 1).

Of the three CIOMS requirements, "impracticability" is likely to be the most difficult for RECs to assess and is clearly a sensitive and contentious topic. History reveals that waivers of consent were originally conceived to studies that could not be conducted if informed consent had to be secured from each participant [11]. Yet, there are data showing that this has changed over time − although affects a very limited number of trials in two different ways. Thus, it has been shown that there are a few trials that a) enrolled most participants after their informed consent was sought but completed the recruitment process enrolling less than 10% of participants without consent; or b) trials that sought consent from all subjects (or legally authorized representatives) at some sites, but waived consent of participants enrolled at other sites [12].

RCTs with pragmatic aims are increasingly popular to assess any type of intervention. Among 1,988 of this type of trials published in 2014–2019, 8% (n = 165) waived participants' consent [13]. Waiver of consent seems to be increasing and is associated with cluster randomization and pragmatic aims −although none of these features justify, per se, waivers for consent [13]. However, trials registered on the EU-Clinical Trials Register has shown that the number of low-intervention RCTs (or low-risk pragmatic RCTs) that could have fulfilled the three CIOMS ethical requirements to have the informed consent process modified or waived is very small: 8 out of 420 (1.9%) phase 4 ongoing RCTs in 2016–2018 [14]. Including waivers of consent in the next revision of the Declaration of Helsinki, would recognize the permissibility of this practice in particular cases but also provide an opportunity to reiterate that such waivers should not be offered where they do not meet relevant conditions—such as those articulated in CIOMS guidelines [2].

Although RECs of any country have the right to approve modifications and waivers of consent in any trial even if the national regulations do not contemplate it [15], the next revision of the Declaration of Helsinki, should consider including this possibility for research in competent participants. Ideally, the wording should be like that of the CIOMS guidelines, as it includes the key relevant requirements to consider and is short enough to be in line with the way the items of the Declaration of Helsinki are worded. This will allow clinical investigators from all over the world the explicit ethical support to propose these exemptions in certain types of research.

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Data availability statement All data is provided in the manuscript.

Declarations

Conflicts of interest The author declares no conflicts of interest.

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