Waiver of consent for low-risk studies

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In the current issue of the *Journal*, Topolovec-Vranic et al (1) (pages 293-296) report on the use of deferred/waived consent in a minimal-risk study involving cognitively impaired patients. Twenty-seven patients were eligible and only three surrogate decision-makers (SDMs) refused participation. In the other cases, there were no secondary withdrawals after the initial consent had been provided. It is certainly good news that patients or SDMs readily grant their consent for such a study. Because the study was performed in one intensive care unit, with 'real' critically ill patients and families, these results are convincing, whereas most published research in this field uses questionnaires in artificial scenarios. It will provide fuel to those who struggle to obtain more flexibility for legislation on human research from lawmakers and regulators. There are three conditions that could justify a waiver of consent before starting a research study using human participants.

The first concerns the observational nature of research (2,3). Observational studies are usually designed using 'noninterventional' methods, meaning that the research adds no extra intervention to the usual care of the patients/participants. This is crucial because consent is commonly not required for most observational studies aside from, of course, the specific regulation concerning data protection. In this study, the majority of the blood samples were collected during routine care ('le tube en plus', in French), but one out of six was not. As mentioned in the conclusion, this research should accordingly be defined as 'minimally interventional'. In the dangerous world of intensive care, any additional collection of blood from indwelling catheters exposes patients to nosocomial infection. Accordingly, manipulations of intravenous or arterial lines are severely limited. In this context, most European research ethics committees would have considered the study to be interventional, and would have required consent from the patient or SDM.

An emergency situation is another common reason for permitting the waiver of consent (4,5). To establish baselines for serum markers, Topolovec-Vranic et al (1) needed to obtain blood samples from patients immediately on admission. In this context, 'emergency' is not due to the urgency for starting treatment, but is dictated by the urgency to start research. Authors define the study as 'time sensitive' and explain that the study cannot be performed if prior consent is not waived. The Canadian Tri-Council Policy statement (TCPS) (article 3.8) clearly authorizes the waiver of consent for emergency research. However, this defines clinical emergencies as situations when patients' lives are immediately threatened, such as acute respiratory or cardiac failures, cardiac arrest and states of shock, as well as strokes. Currently, no legislation contains provisions permitting waiver of prior consent due to the urgency to start research. However, solving this issue is possible in Canada by using TCPS-2, article 37.7 (c), when "...it is impossible or impracticable to carry out the research ..." Similarly, this provision may apply to cluster trials, allowing the waiver of individual consent when entire groups of individuals are randomized (6).

Third, prior consent could be waived in minimal-risk trials. Again, this is a matter of endless debate, re-emerging each time legislation on biomedical research is revised (7,8). Investigators, bioethicists, lawmakers and regulators repeatedly challenge identification of a low-risk category of research with more flexible provisions. One major tenet of ethics and regulation on humane research is certainly the obligation to obtain informed consent before any trial can be started, in a 'one size

fits all' manner. The code of Nuremberg did not foresee anything resembling 'low-risk' research; neither did the declaration of Helsinki nor the Oviedo convention in Europe. Investigators who claim that consent modalities in low-risk research should be adapted find it difficult to convince institutional review boards or legislators to allow it. The European directive 2001/20/CE, in force in all European member states since 2004, did not mention anything about low-risk research. The omission was corrected in May 2014 when a new regulation was adopted that repealed the directive (9) and a category of 'low-intervention' research was finally inserted into the legislation. However, prior written consent remains mandatory. Except for cluster trials, the issue of authorizing a kind of 'facilitated consent' was not even addressed. In France, the legislation of 2004 has defined a new category of low-risk research called research on 'usual care', which may not apply to research on drugs. Consent was replaced by the obligation of information to the participants and the right for them to opt out. However, in 2012, when the law was revised once again, consent was reintroduced, although may possibly be given orally. The United States federal code authorizes the waiver/deferral of consent for minimal-risk studies provided several conditions are fulfilled (45 CFR 46 [d]), unlike the Canadian Tri-Council Policy (article 3.7 of TCPS-2), which does not permit it clearly.

Indeed, altering the ways 'informed consent' is granted or waived for low-risk research has proven to be extremely difficult. The study by Topolovec-Vranic et al (1) suggests that the addition of several conditions – low risk, time-sensitive study, minimally interventional, critical illness – should enable the use of deferred/waived consent. Law-makers and regulators remain to be convinced.

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