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EDITORIAL

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Research to inform the consent-to-research process

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Critically ill patients are often incapable of providing first-person research consent at the time that they meet eligibility criteria for study interventions, either due to the nature of their underlying critical illness or to the treatments that they require. To ensure that science and knowledge can continue to advance while respecting the ethical principle of autonomy, we commonly asked substitute decision-makers (SDMs) to provide consent on patients' behalf [1, 2]. In situations where a study is deemed to pose only minimal risk, for example, observational studies, some research ethics boards may waive the need for informed consent, although the criteria used to establish minimal risk have varied [3, 4]. Studying interventions that must be administered on an emergency basis can further complicate the informed consent process due to the inability to identify SDMs within a suitable time frame [5]. Delayed consent is an approach that has been increasingly used to allow incapable patients to participate in emergency research. It involves enrolling patients into a study before consent is obtained, but then later approaching either the patient or the SDM to obtain consent for ongoing participation and use of data. While the acceptability of this approach to patients has been a topic of research and debate, one thing is certain: delayed consent can facilitate dramatic increases in study enrolment when SDMs are not immediately available [6].

Strategies for enrolling incapable critically ill patients who are unable to consent to research participation (Table 1) must follow established ethical principles and should also consider the impact of such participation on critically ill patients and their relatives. Indeed, whether or not critically ill patients and their SDMs endorse the SDM model and/or delayed consent approaches has been explored in several recent publications [7–10]. The overarching theme that has emerged is that patients and their relatives generally want to be involved in the research decision-making process where feasible, even though this may contribute additional anxiety [11].

Gigon and colleagues [12] contribute to this evolving area of knowledge in a study published in a recent issue of *Intensive Care Medicine*. They surveyed pairs of patients and their relatives at the time of discharge from the intensive care unit to determine their opinions about informed consent for research. Each pair was randomly assigned to receive a vignette describing either a "non-invasive" chart review study or an "invasive" randomized controlled trial. The authors received responses from 185 (40 %) patients and 125 (68 %) SDMs. While this methodology precludes a direct comparison of the same individual's opinions about consent for the two different study designs, the majority (69–75 % overall) of respondents preferred that patients provide first-person informed consent when feasible, or that a relative provide

Table 1 Strategies for enrolling incapable, critically ill patients unable to consent to research participation

Strategy	Advantages	Disadvantages
No research while patient is incapable	Protects incapable patient from possible harm associated with research participation	Patients may not regain capacity until they are no longer eligible Advances in knowledge on critical illness becomes difficult or in some situations even impossible Discriminates against critically ill patients by denying them the opportunity to participate in research
Advanced consent prior to critical illness and/or eligibility	Ensures patients agree to research participation prior to enrolment in situations where research eligibility is anticipated (e.g. following elective surgery)	Seldom feasible due to unpredictable and/or urgent nature of many critical illnesses Involves consenting patients that may subsequently be deemed ineligible to participate
Waiver of need for informed consent (following approval by institutional review board)	Research can involve all eligible but incapable patients Research can be conducted in emergency situations where time constraints render obtaining prior informed consent infeasible	Exposes incapable patients to possible harms associated with potentially unwanted research participation Makes no attempt to incorporate patients' own opinions about research participation
Enrolment followed by delayed/deferred consent by patient once capacity is regained	Research can involve all eligible but incapable patients, but also allows patients to opt out of ongoing participation once they have regained capacity	Exposes incapable patients to possible harm associated with potentially unwanted research participation Threatens internal validity if post-randomization opt-outs lead to differential follow-up or data availability across study groups May limit generalizability if a large proportion of patients opt out
Consent from substitute decision-maker (SDM)	Research can involve eligible but incapable patients for whom prior consent is obtained from SDMs Preserves patient autonomy if SDMs can approximate the patients' own preferences regarding research participation Appears to be preferred by patients	May add additional burden to already stressed and anxious SDMs Typically results in reduced enrolment compared to other consent strategies Inaccurate proxy estimates of incapable patients' preferences can still expose them to possible harms associated with potentially unwanted research May limit generalizability if a large proportion of SDMs do not provide consent

consent during the time the patient was unconscious (52–63 % overall). A majority of respondents also appeared to endorse both the deferred consent approach, or "consent in two steps" (i.e. a short description and enrolment if no objection, followed by formal consent and full information at a later time). These findings provide additional reassurance that currently adopted practices are acceptable to most patients.

However, Gigon and colleagues also observed that more than one-third (37 %) of the subgroup of patients who were unaccompanied by a relative indicated their preference to involve their family doctor when considering the randomized controlled trial, compared to only 13 % of their counterparts when considering the chart review study. Indeed, many respondents indicated a preference for having more than one individual involved in the consent process, regardless of whether the patient was conscious (36–58 %) or unconscious (36–60 %). The authors acknowledge that respondents to their survey may have been more favorably predisposed to research than non-respondents and that therefore the results may underestimate how many would have preferred to involve additional individuals. These findings suggest that researchers could consider helping critically ill patients or their families to obtain external advice and opinions about study participation, especially for studies that pose more than minimal risk of harm. They also underscore the uncertainty and discomfort that may be associated with decision-making during critical illness and reinforce previous observations that requesting informed consent for research can place an additional burden on already distressed family members [10, 13].

A frequent frustration for many researchers arises from the variable interpretations by research ethics boards and regulatory bodies regarding the appropriateness or acceptability of waived and delayed consent (or even of conducting any research at all when study participants are incapable) [14, 15]. Furthermore, researchers and research

ethics boards alike also often have difficulty establishing the thresholds for risk that should be deemed acceptable for studies using a waiver of consent or delayed consent, what truly constitutes an "emergency treatment" and even establishing when the requirement for equipoise has been established [16–21]. Studies like the one conducted by Gigon and colleagues are essential for helping physicians refine and improve the process for obtaining informed consent so that investigations involving critically ill patients can continue while their autonomy remains protected. Research of this type can be used to help inform research ethics boards about patients' preferences for particular approaches to consent. Ongoing controversies may further complicate the ethics approval process such as, for example, when should informed consent be required for cluster randomized trials or for research involving planned quality improvement initiatives [22–24]. In addition to education and advocacy, the scientific community's response to these challenges should be to obtain additional empirical evidence from patients, relatives, and other stakeholders—like the study conducted by Gigon and colleagues—that can help inform the debate and improve how we conduct critical care research.

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Conflicts of interest None.

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