PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	ADVANCE CONSENT FOR PARTICIPATION IN RANDOMIZED CONTROLLED TRIALS FOR EMERGENCY CONDITIONS: A SCOPING REVIEW
AUTHORS	Niznick, Naomi; Lun, Ronda; Dewar, Brian; Perry, Jeffrey; Dowlatshahi, Dar; Shamy, Michel

VERSION 1 – REVIEW

REVIEWER	William B. Feldman Harvard Medical School
REVIEW RETURNED	21-Sep-2022

GENERAL COMMENTS	This is a comprehensive and helpful examination of advance directives for research in emergency settings. The investigators performed a rigorous systematic review of the literature and clearly described their findings. Major 1. The biggest limitation of this review, as the authors acknowledge, is the paucity of literature on advance directives for research in emergency settings. This is no fault of the authors; their review was thorough. But there simply has not been much written on the topic. 2. The authors included only papers related to emergency clinical research. They note (page 5, line 51-52): “Studies focusing on advance care planning…for research into non-emergency conditions…were excluded.” However, 2 of the 6 articles included in the review appear to involve non-emergency conditions. The authors do not offer a clear definition of what constitutes emergency research, but they suggest in several places that key components are (1) a narrow window for intervention and (2) the fact that patients are often incapacitated. The author write (page 5, lines 9-12): “Emergency research presents unique challenges to obtaining informed consent because decision-making needs to happen quickly, patients may be incapacitated...” These two features are certainly characteristic of stroke and intraparenchymal hemorrhage (the 2 examples that the authors mention) and also true for other paradigmatic examples of emergency research (cardiac arrest, hemorrhagic shock, respiratory failure). However, 2 articles seem to involve conditions lacking these one or both of these features: (1) The article by Corneli at al. examined hospital acquired pneumonia (HAP). Many patients with HAP are perfectly capable of consenting, and the time window for intervention is longer than for the other paradigmatic examples. (2) The article by Backlar et al. examined schizophrenia, where patients are incapacitated but without the need for rapid intervention. Among trials granted exceptions from informed

	consent (EFIC) in the United States, for example, none have been granted for pneumonia or schizophrenia (but have been granted for ischemic stroke, traumatic brain injury, cardiac arrest, hemorrhagic shock, respiratory failure, seizures, and others). At a minimum, I think the authors should provide more detail about why they consider pneumonia and schizophrenia to be emergencies in the relevant sense. However, I worry that these articles may need to be excluded, in which case the number of articles in the review would drop to just 4, further heightening the concerns raised in critique #1 above. Minor 1. I would like to see more about the status of advance directives for research. Suppose that a patient has an advance directive agreeing to enrollment in a clinical trial and is incapacitated at presentation. If a surrogate decision-maker objects to enrollment in the clinical trial, would the research team defer to the proxy? Is there relevant ethical and/or legal guidance here? 2. I would like to see more about the distinction between enrolling in a particular trial (e.g., the agitation study) and more general research directives. How do these differ ethically and legally? 3. There is an interesting parallel to opt-out wristbands in EFIC trials. Many EFIC trials hand out wristbands to people who wish to opt out in case they might be enrolled without their consent in the future. Like advance planning for future enrollment, wristbands represent advance planning for future refusal. This, of course, goes beyond the scope of the review. But, space permitting, this may be an interesting angle to explore in the discussion. 4. Also in the discussion, it may worth mentioning community consultation in the setting of EFIC. All EFIC trials in the US have to engage in community consultation prior to starting their studies, and investigators often conduct surveys asking participants their views about enrollment without consent. These, of course, are surveys, not consent procedures. But it may be interesting, space permitting, to discuss the differences, particularly since the studies included are US-focused.

REVIEWER	Tomasz Pietrzykowski University of Silesia, Research Centre for Public Policy and Regulatory Governance, Faculty of Law and Administration
REVIEW RETURNED	31-Oct-2022

GENERAL COMMENTS	The paper is interesting but needs some revisions. In particular it is unclear whether so heterogenic papers are appropriate material for scoping review aiming at the examination of literature on the use of advance consent in emergency conditions. If the authors intend to examine papers on RCTs based entirely or partially on advance consent - the scope seems sufficient (although their search suggests that there was only one such RCT, that was finally unsuccessful). If they plan to discuss the literature as such on advance consent (including legal, ethical or policy aspects) further journal/books databases could be relevant. The final outcome of the paper includes all papers the author found that discuss advance consent in RCT, but the scope of searched databases makes it doubtful whether they can be trusted as complete. Additionally, the outcomes are rather outdated (to include papers before 2020 only), while the

	advance consent may be a much more intensely discussed topic in the recent three years (whether or not it means additional RCTS actually using such consent). Furthermore, advance consent is still a relatively vaguely defined term and the authors should take into account whether the papers from a time span of 25 or 27 years use the term consistently and make sure they examined the papers with respect to the conceptual consistency of problems discussed therein.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. William B. Feldman, Harvard Medical School, Brigham and Women's Hospital
Comments to the Author:
This is a comprehensive and helpful examination of advance directives for research in emergency settings. The investigators performed a rigorous systematic review of the literature and clearly described their findings.

Major

1. The biggest limitation of this review, as the authors acknowledge, is the paucity of literature on advance directives for research in emergency settings. This is no fault of the authors; their review was thorough. But there simply has not been much written on the topic.

Thank you for your comment. We appreciate your acknowledgement that our methods were thorough. Ultimately, we do not see the conclusion that little work has been done in this area as a limitation of the work; rather, it is the nature of a scoping review to map the extent of the literature on a given topic, be that large or small. We hope that the paper will provide a strong review on the literature to date and will encourage further research to be done on this very interesting topic.

2. The authors included only papers related to emergency clinical research. They note (page 5, line 51-52): “Studies focusing on advance care planning…for research into non-emergency conditions…were excluded.” However, 2 of the 6 articles included in the review appear to involve non-emergency conditions. The authors do not offer a clear definition of what constitutes emergency research, but they suggest in several places that key components are (1) a narrow window for intervention and (2) the fact that patients are often incapacitated. The author write (page 5, lines 9-12): “Emergency research presents unique challenges to obtaining informed consent because decision-making needs to happen quickly, patients may be incapacitated...” These two features are certainly characteristic of stroke and intraparenchymal hemorrhage (the 2 examples that the authors mention) and also true for other paradigmatic examples of emergency research (cardiac arrest, hemorrhagic shock, respiratory failure). However, 2 articles seem to involve conditions lacking these one or both of these features: (1) The article by Corneli at al. examined hospital acquired pneumonia (HAP). Many patients with HAP are perfectly capable of consenting, and the time window for intervention is longer than for the other paradigmatic examples. (2) The article by Backlar et al. examined schizophrenia, where patients are incapacitated but without the need for rapid intervention. Among trials granted exceptions from informed consent (EFIC) in the United States, for example, none have been granted for pneumonia or schizophrenia (but have been granted for ischemic stroke, traumatic brain injury, cardiac arrest, hemorrhagic shock, respiratory failure, seizures, and others). At a minimum, I think the authors should provide more detail about why they consider pneumonia and schizophrenia to be emergencies in the relevant sense. However, I worry that these articles may need to be excluded, in which case the number of articles in the review would drop to just 4, further heightening the concerns raised in critique #1 above.

Thank you for your comment. You are absolutely right that in the original manuscript we did not provide a specific definition of emergency conditions, and this is an important weakness of that paper as submitted. We have sought to address your important concern. In conducting our search, we used the following operational definition of an emergency condition in the course of our search and have now included it in the methods. From our point of view, an emergency condition was one that required the initiation of investigations or treatment (and hence the decision about research participation) quickly including in severely ill hospitalized patients and in the emergency department. We have included this definition in the manuscript on page 5, at the end of the last paragraph.

We believe that severe pneumonia and a psychotic episode would both qualify under this definition, which is why we included them in our analysis. Papers we reviewed but excluded on the basis of referring to non-emergency conditions included dementia and other progressive neurological diseases. We also excluded papers related to emergency conditions where consent was in the non-emergency phase, ie after patients with subarachnoid hemorrhage or brain trauma had been admitted to hospital and already received acute treatment. We also excluded papers related to emergency conditions but where the patient was in the pediatric population, such as one paper exploring consent for research in children with Sickle Cell crisis.

Minor

1. I would like to see more about the status of advance directives for research. Suppose that a patient has an advance directive agreeing to enrollment in a clinical trial and is incapacitated at presentation. If a surrogate decision-maker objects to enrollment in the clinical trial, would the research team defer to the proxy? Is there relevant ethical and/or legal guidance here?

Thank you very much for this interesting question. Indeed, in the course of developing the feasibility of an advance consent model, we will need to address exactly these kinds of practicalities. We have elaborated on this topic in the discussion of the paper. The additional paragraph incorporates your suggestions from minor points 1, 2 and 3. The paragraph is outlined below following comment 3.

2. I would like to see more about the distinction between enrolling in a particular trial (e.g., the agitation study) and more general research directives. How do these differ ethically and legally?

Thank you again for this interesting question. As above, it is important for future research to address these practicalities. We have elaborated on this topic in the discussion of the paper. The additional paragraph incorporates your suggestions from minor points 1, 2 and 3. The paragraph is outline below following comment 3.

3. There is an interesting parallel to opt-out wristbands in EFIC trials. Many EFIC trials hand out wristbands to people who wish to opt out in case they might be enrolled without their consent in the future. Like advance planning for future enrollment, wristbands represent advance planning for future refusal. This, of course, goes beyond the scope of the review. But, space permitting, this may be an interesting angle to explore in the discussion.

Thank you very much for another interesting question. As above, it is important for future research to address these practicalities. We have elaborated on this topic in the discussion of the paper. The additional paragraph incorporates your suggestions from minor points 1, 2 and 3. The paragraph is outline below following comment 3.

The following paragraph has been added to the end of page 12/ beginning of page 13:

Given the little experience with advance consent we were able to identify in this scoping review, many details regarding the practical application of advance consent could not be developed in detail through our search. First, should advance consent be tied to a particular trial protocol only, or should be it be more general and applicable to any available research trial for which a patient may be eligible? While the concept of general or "broad" consent is known in clinical research, it has tended to be used in relation to the future study of tissue samples. It remains to be seen whether physicians, participants, and regulators will feel comfortable with general advance consent (for example, a patient who consents to participate in any acute stroke trial) as a stand-in for specific informed consent (for example, a specific stroke trial). Second, how would advance consent from an incapable patient be prioritized if that patient's substitute decision-maker objects to trial participation? We would expect that a legal, signed, informed consent document from an incapable patient would be considered valid in most legal jurisdictions, even if a legally authorized representative is available. Such an eventuality could in fact be written into an advance consent document. Importantly, it must also be noted that a patient has the right to decline participation in advance, and that such an advance decision should also be respected in the event that they are eligible for participation in a trial. Ultimately, practice regarding some of these issues will be determined by individual jurisdictions' legal standards, which vary quite significantly from country to country, and sometimes even within countries.

4. Also in the discussion, it may worth mentioning community consultation in the setting of EFIC. All EFIC trials in the US have to engage in community consultation prior to starting their studies, and investigators often conduct surveys asking participants their views about enrollment without consent. These, of course, are surveys, not consent procedures. But it may be interesting, space permitting, to discuss the differences, particularly since the studies included are US-focused.

Thank you for your comment. Engaging the community in consultation remains an important step prior to conducting EFIC trials. Given that obtaining advanced consent for participation in research focuses on individual preferences, the authors believe that surveying the community for their viewpoint on specific trials may fundamentally not be necessary. However, future studies assessing the overall acceptance of advance consent for research is very important in order to better appreciate and understand the public's view on the subject. The importance of pursuing research in this is area is highlighting on page 14, at the end of the first paragraph.

Reviewer 2 Comments

Reviewer: 2
Dr. Tomasz Pietrzykowski, University of Silesia

Comments to the Author:
The paper is interesting but needs some revisions. In particular it is unclear whether so heterogenic papers are appropriate material for scoping review aiming at the examination of literature on the use of advance consent in emergency conditions. If the authors intend to examine papers on RCTs based entirely or partially on advance consent - the scope seems sufficient (although their search suggests that there was only one such RCT, that was finally unsuccessful). If they plan to discuss the literature as such on advance consent (including legal, ethical or policy aspects) further journal/books databases could be relevant. The final outcome of the paper includes all papers the author found that discuss advance consent in RCT, but the scope of searched databases makes it doubtful whether they can be trusted as complete. Additionally, the outcomes are rather outdated (to include papers

before 2020 only), while the advance consent may be a much more intensely discussed topic in the recent three years (whether or not it means additional RCTS actually using such consent). Furthermore, advance consent is still a relatively vaguely defined term and the authors should take into account whether the papers from a time span of 25 or 27 years use the term consistently and make sure they examined the papers with respect to the conceptual consistency of problems discussed therein.

Thank you for these comments.

We understand a scoping review to be an effort to map any and all literature pertaining to a particular topic. In this case, we sought to identify any and all experience or commentary regarding advance consent for emergency research. We did not intend to limit our analysis to RCTs that had used advance consent, though as you point out we did find two such instances, and their experiences are of central importance to our analysis. As you note, there was a significant literature on advance consent, and on emergency research. We screened over 1000 manuscripts to identify the few that met our criteria.

Regarding the definition of advance consent, we used an operational definition in which we sought any experience in which a potential research participant provided consent to participate in research (be it a single study or any research) in advance of fulfilling the criteria for that research study. As described above, an emergency condition was one that required the initiation of treatment (and hence the decision about research participation) quickly and in the emergency department. An eligible condition was one that rendered the patient incapable of providing her or his own consent at that time. We have clarified our definitions in the manuscript on page 5, at the end of the last paragraph.

We acknowledge that our search was conducted in 2020, and that more research may have been published since on the topic of advance consent. As we are actively publishing in this area, we have not encountered any manuscripts in the last few years that would change the results of our review in an important way. A pubmed search of "advance consent" and "preconsent" in 2021 and 2022 reveals no manuscripts that relate to our topic. Recently published research on models of consent for emergency research (see references below) have not directly addressed advance consent.

VERSION 2 – REVIEW

REVIEWER	William B. Feldman Harvard Medical School
REVIEW RETURNED	15-Dec-2022

GENERAL COMMENTS	The authors have addressed my concerns.