




BMJ Open Advance consent for participation in randomised controlled trials for emergency conditions: a scoping review

Naomi Niznick ¹, Ronda Lun ¹, Brian Dewar ², Jeffrey Perry,^{2,3}
Dar Dowlatshahi,^{1,2} Michel Shamy^{1,2}

To cite: Niznick N, Lun R, Dewar B, *et al.* Advance consent for participation in randomised controlled trials for emergency conditions: a scoping review. *BMJ Open* 2023;**13**:e066742. doi:10.1136/bmjopen-2022-066742

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-066742>).

Received 18 July 2022

Accepted 15 January 2023



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

¹Division of Neurology, Department of Medicine, Ottawa Hospital, Ottawa, Ontario, Canada

²Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

³Department of Emergency Medicine, Ottawa Hospital, Ottawa, Ontario, Canada

Correspondence to

Dr Naomi Niznick;
naniznick@toh.ca

ABSTRACT

Objective Advance consent is a recognised method of obtaining informed consent for participation in research, whereby a potential participant provides consent for future involvement in a study contingent on qualifying for the study's inclusion criteria on a later date. The goal of this study is to map the existing literature on the use of advance consent for enrolment in randomised controlled trials (RCTs) for emergency conditions.

Design Scoping review designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses–Extension for Scoping Reviews guidelines.

Data sources We searched electronic databases including MEDLINE, Embase, Web of Science and the Cochrane Register of Clinical Trials from inception to 10 February 2020.

Eligibility criteria Eligible studies included articles that discussed or employed the use of advance consent for enrolment in RCTs related to emergency conditions. There were no restrictions on the type of eligible study. Data were extracted directly from included papers using a standardised data charting form. We produced a narrative review including article type and authors' dispositions towards advance consent.

Results Our search yielded 1039 titles with duplicates removed. Six articles met inclusion criteria. Three articles discussed the theoretical use of research advance directives in emergency conditions; one article evaluated stakeholders' perceptions of advance consent; and one article described a method for patients to document their preferences for participation in future research. Only one study employed advance consent to enrol participants into a clinical trial for an emergency condition.

Conclusion Our review demonstrates that there has been minimal exploration of advance consent for enrolment in RCTs for emergency conditions. Future studies could aim to assess the acceptability of advance consent to participants, along with the feasibility of enrolling research participants using this method of consent.

Protocol The protocol for this scoping review was published a priori.

INTRODUCTION

Informed consent, in which a patient agrees to participate in research after having received a thorough explanation of the potential risks and benefits, is a fundamental component of

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This scoping review outlines a novel approach to obtaining consent for enrolment in randomised controlled trials.
- ⇒ We systemically summarised the literature using broad inclusion criteria which did not restrict the type of publications included in this scoping review.
- ⇒ This review is limited by there being little literature available on this topic.
- ⇒ Given the heterogeneity of study types included in our analysis, there is inherent risk of bias.

modern clinical research. Emergency research presents unique challenges to obtaining informed consent because decision making needs to happen quickly; patients may be incapacitated; and patients and their family members may be severely distressed.^{1–3} These challenges have been increasingly recognised in the design of trials for emergency neurological conditions such as acute ischaemic stroke and intracerebral haemorrhage, where patients are almost universally incapable of providing consent and enrolment decisions need to happen on a scale of minutes.^{4 5} Several methods have been employed to try to address the challenge of informed consent in research with incapacitated patients under emergency circumstances. In some instances, patients may be enrolled into randomised controlled trials (RCTs) with consent from a substitute decision maker (SDM).⁶ Other potential methods of enrolment include waiver of consent and deferral of consent, where a patient is enrolled into a study immediately and efforts are made to obtain consent after the fact, either from the patient or from an SDM.^{7–9} Availability and acceptability of approaches to consent may vary, depending on legal or cultural factors.^{6 10 11}

Advance consent for enrolment in RCTs for emergency conditions is a potential method to overcome the challenges of obtaining informed consent. Advance consent for

research occurs when a potential participant provides consent for future involvement in a study, contingent on qualifying for the study's inclusion criteria at a later date, for example, when the participant no longer has capacity.^{12 13} Advance consent may be specific to a particular trial, may detail a patient's wishes concerning participation in specific types of studies or may be a reflection of values to guide researchers about the patient's desire to participate in research. American and Canadian guidelines specifically allow for advance consent; the Canadian TCPS2 statement explicitly requires researchers and authorised parties to be guided by these directives.¹⁴ Historically, advance consent has mainly been used for research in predictably progressive diseases, such as Alzheimer's dementia.^{15–18} Though advance consent may appear challenging to apply to emergency conditions, given their unpredictable nature, it may be possible to identify patients at risk of suffering from specific emergency conditions based on the presence of recognised risk factors (eg, patients seen in a cardiology clinic with coronary artery disease who are at risk of developing acute coronary syndrome, patients seen in a stroke prevention clinic who are at risk of suffering an acute ischaemic stroke or patients with epilepsy seen in a general neurology clinic who are at risk of presenting with status epilepticus). Inviting them to provide advance consent for research could alleviate many limitations of current consent practices for emergency research.

With these issues in mind, we aimed to review the existing literature on the use of advance consent for enrolment in RCTs for emergency conditions and to secondarily describe the use of advance consent specifically for emergency neurological conditions.

METHODS AND ANALYSIS

We conducted a scoping review to search the literature for experiences with advance consent for participation in RCTs for emergency conditions.¹⁹ A detailed protocol of the study design and methods was developed and published a priori.¹⁹ This scoping review was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses–Extension for Scoping Reviews guidelines.²⁰ It was conducted using the

framework of Arksey and O'Malley and further defined by Levac *et al.*^{21 22}

Information sources and search strategy

We performed a search of MEDLINE, Embase (Embase Classic+Embase), Cochrane Central Register of Controlled Trials and Web of Science from inception to 10 February 2020. We developed a structured search strategy in consultation with a health science librarian. Controlled vocabulary and relevant key terms were used. Reference lists of included studies were reviewed for potential inclusion. The full search strategies are outlined in online supplemental table 1.

Eligibility criteria and study selection

Research articles were selected for inclusion if they discussed, in any manner, the use of advance consent for participation in RCTs on emergency conditions and/or treatments. An emergency condition was defined as one that required the initiation of investigations or treatment quickly, including in severely ill hospitalised patients and in the emergency department (ED). We included articles with adult patients 18 year or older, published in English. Articles were not restricted based on study design. Studies focusing on advance care planning in areas other than research, or for research into non-emergency conditions, and those exclusively discussing other variations on informed consent were excluded. Abstracts and letters to the editor were additionally excluded (table 1).

We used Covidence (Covidence, Melbourne) to screen citations for inclusion at the title, abstract and full-text level.²³ Citations were screened independently by at least two trained reviewers (NN and RL). Reviewers met to resolve discrepancies after 25% of the title and abstract citations had been screened. Citations advanced to the next step of review after agreement between the two independent reviewers. Conflicts were resolved by consensus or a third-party independent reviewer (NN and RL). Reference lists of included full-text articles were reviewed for further relevant publications.

Data extraction and charting

We retrieved the full texts of included studies, and the data were extracted by two independent reviewers

Table 1 Inclusion and exclusion criteria

Criteria	Inclusion	Exclusion
Language	English	Any other language
Type of article	RCTs, observational studies, systematic reviews, narrative reviews, surveys, interviews, ethics papers	Letters to the editor, abstracts
Age	18 years or older	Younger than 18 years old
Population	Emergency conditions and/or treatment	<ul style="list-style-type: none"> ▶ Non-emergency conditions, such as dementia, and non-emergent treatment. ▶ Pregnancy.
Topic of interest	Advance consent for participation in RCTs	<ul style="list-style-type: none"> ▶ Other forms of consent such as deferred consent or waiver of consent. ▶ Advance care planning in areas other than research such as medical care, treatment and advance consent for end-of-life care.
RCT, randomised controlled trial.		

(NN and RL) onto a standardised data charting form (online supplemental table 2). Conflicts were resolved by consensus. Descriptive data were extracted on the article and author including the journal title, year of publication, type of author (MD, PhD or other) and publication country of origin. Data on the paper characteristics, methodology, medical condition of interest and method of employing advance consent for research were also obtained. Specifically, we extracted the type of research paper, the medical condition of focus, whether the medical condition was neurological, the author's position on the use of advance consent for research, and any statements explaining how advance consent was used or discussed in the paper. If the paper was a clinical study, we recorded whether advance consent was used to enrol participants.

Analysis

Given the anticipated heterogeneity of study methodology and expected varying use of advance consent in eligible studies, we performed a narrative review with descriptive analysis. Data were synthesised with thematic grouping. Quantitative analysis was not planned.

Patient and public involvement

Patients and the public were not directly involved in the design or dissemination plan of this research project.

RESULTS

Search results

Our electronic database searches yielded 1532 studies. With duplicates removed, 1039 titles and abstracts were screened, and 29 full-text articles were reviewed. No additional publications were included after reviewing the reference lists. Six articles met the inclusion criteria (figure 1).

Article characteristics

The six articles were published from 1995 to 2019. All of the articles were from the USA. They were heterogeneous in their methodologies, medical conditions studied, and methods of using, evaluating or describing advance consent for research. Two of the articles were commentaries^{24 25}; one was a consensus statement²⁶; one consisted of semistructured interviews²⁷; one was a historical review²⁸; and one was a cohort study.²⁹ Specific conditions

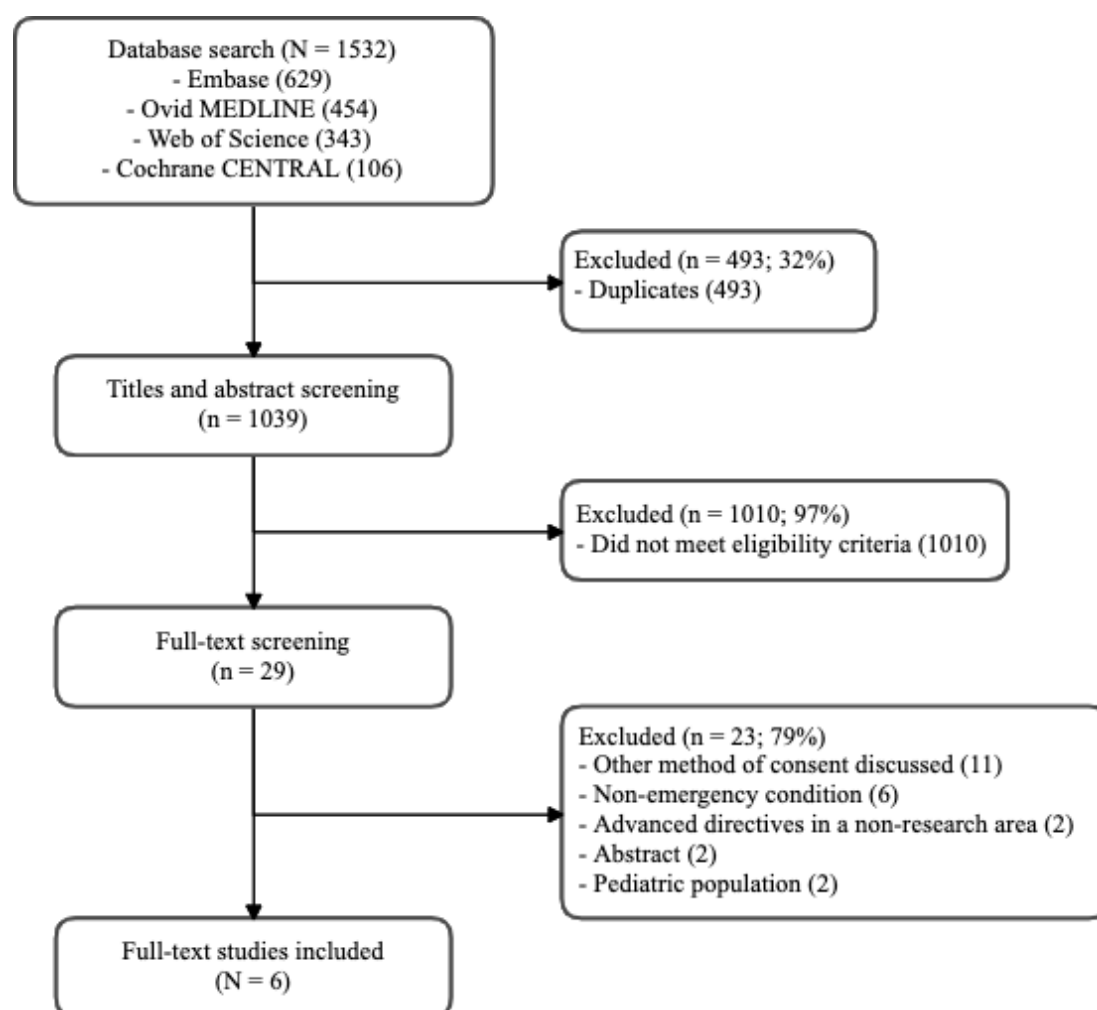


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

Table 2 Characteristics of included articles

Author	Year	Country	n	Type of article	Condition	Description of use of advance consent
Backlar ²⁴	1999	USA	369	Commentary	Psychiatric: schizophrenia	Author discusses the theoretical use of research advance directives.
Biros <i>et al</i> ²⁶	1995	USA	303	Consensus statement	No specific condition mentioned: 'emergency conditions'	Authors discuss the theoretical use of research advance directives in the context of federal regulations in the USA.
Cole <i>et al</i> ²⁹	2019	USA	1165	Cohort	Psychiatric: agitation	Authors employ the use advance consent for enrolment in an randomised controlled trial. Observational cohort study of patients screened and who consented in advance for potential future enrolment in a randomised trial examining treatments for acute agitation in the emergency department.
Corneli <i>et al</i> ²⁷	2018	USA	1095	Interview	Respiratory: pneumonia	Authors interview stakeholders to determine the perceived acceptability of the use advance consent for enrolment in a theoretical RCT.
Karlwish <i>et al</i> ²⁸	1997	USA	340	Historical review	No specific condition mentioned: emergency medicine	Authors explain research advance directives and discuss the ethics and regulations in the USA concerning the use of advance consent for research on emergency conditions.
McGehrin <i>et al</i> ²⁵	2018	USA	811	Commentary	Neurological: ischaemic stroke	Authors outline the use of a standardised document which allows patients to record their preferences regarding acute stroke treatment interventions, as well as for preferences for participation in future stroke clinical trials.

addressed included acute psychiatric illnesses (n=2),^{24 29} pneumonia (n=1)²⁷ and stroke (n=1).²⁵ Two articles did not mention specific conditions^{26 28} but rather addressed emergency conditions in general. Three articles discussed the theoretical use of research advance directives in emergency conditions.^{24 26 28} One article used semistructured interviews to determine stakeholders' perceptions of the use of advance consent for enrolment in an RCT for the treatment of pneumonia.²⁷ One article described a method for patients to document their preferences for participation in future research as part of a broader approach to advance directive for patients who had a stroke but did not elaborate on advance consent specifically.²⁵ Only one study reported using advance consent to enrol participants into a clinical trial (table 2).²⁹

Arguments for and against the use of advance consent for research

Three articles expressed opinions in favour of using advance consent for research^{24 25 27}; two were critical of its use^{26 29}; and one did not mention an opinion (table 3).²⁸ The arguments in favour of advance consent were that it is acceptable to patients²⁷ and that it enhances patient autonomy.^{24 25} The arguments against advance consent were that it was not feasible,^{26 29} that participants would not be adequately informed²⁶ and that it would not protect patients from the risks of participation in RCTs.^{26 29} One article did not mention an opinion regarding the use of advance consent for research and instead defined research advance directives, discussed the ethical considerations and outlined the current regulations in the USA.²⁸

Experiences with advance consent

Corneli *et al* was the only study to report the results of empirical research in that they conducted semistructured interviews with 52 stakeholders, including patients, caregivers, institutional review board representatives, clinical investigators and study coordinators, about advance

consent.²⁷ Stakeholders, including patients and caregivers, reported no concerns about being approached in advance regarding participation in a research study prior to developing the condition required for enrolment, in this case, pneumonia. The authors therefore concluded that an early enrolment strategy with advance consent would be acceptable.

Cole *et al* presented the sole experience using advance consent for study enrolment.²⁹ The authors conducted an observational cohort study of psychiatric participants preconsented for an RCT examining treatments for acute agitation in the ED. Eligible participants provided informed consent for enrolment in the RCT, which involved having a drug administered for agitation in the event that they would present to the ED within the next 3 years with acute agitation. Potential participants could also be consented for the trial in real time, if they retained capacity to provide informed consent or if a legally authorised representative was present to provide consent. Over 1000 patients were screened for the study, and only 75 were found to be eligible to provide advance consent, 43 of whom did provide advance consent. No participant was enrolled into the study via advance consent, and only two participants were successfully enrolled into the trial by other methods of consent. The trial was terminated early, 1 month after enrolling its first patient, due to loss of funding. Given that no participant was enrolled by advance consent, the authors concluded that it was not a feasible approach to study enrolment.

Advance consent and emergency neurological conditions

The article by McGehrin *et al* was the only paper that specifically focused on neurological conditions. McGehrin *et al* proposed a four-page advance directive document they call 'Coordinating Options for Acute Stroke Therapy', which is designed to allow patients to document their preferences regarding acute stroke treatment, including participation in future clinical stroke trials.²⁵ The article

Table 3 Author's disposition on the use of advance consent for research

Author	Author's disposition	Description of supporting evidence
Backlar ²⁴	In favour of use of advance consent for research	The author reasons that 'substantive and procedural research advance directives allow potential subjects to make a choices of their own as to whether they wish to be enrolled and participate in a research protocol, to appoint a surrogate decision maker of their own choosing, and to additionally spell out specific safeguards' and that 'research advance directives provide potential subjects with the opportunity not only to make choices of their own but provide a mechanism that guarantees them a cluster of important protections'.
Biros <i>et al</i> ²⁶	Against use of advance consent for research	The authors contend that 'patients may not consider consent carefully when the changes of entry into a specific study are remote. Thus, they may not be adequately protected from research risks'. Regarding advance consent at hospital admission for a potential future research protocol, the authors argue that preconsent 'cannot be used for emergency research in the prehospital setting or for studying the treatment of acute illnesses that occur in the out-of-hospital setting'. Regarding obtaining advance consent from unaffected subjects who may require emergency care in the future, the authors argue that 'identifying those patients who have previously consented may not be feasible when the critical situation occurs'.
Cole <i>et al</i> ²⁹	Against use of advance consent for research	The authors screened 1461 patients for their RCT on loxapine versus IM haloperidol+lorazepam for treatment of acute agitation in the ED secondary to bipolar disorder type 1 or schizophrenia. 'Despite screening >1400 patients and obtaining preconsent in 43 patients', not a single patient was enrolled using preconsent methods. Only two patients were enrolled in the study, and the study was terminated 1 month after enrolment of the first patient due to loss of funding. The article concludes that the use of preconsent in their study was 'found to be infeasible'.
Corneli <i>et al</i> ²⁷	In favour of use of advance consent for research	Structured interviews detail that 'patients and caregivers expressed no concerns about being approached in the ICU about a clinical trial on treatment for pneumonia before the patient was diagnosed with the condition' and that 'the IRB representatives expressed no ethical or regulatory concerns with the early enrollment strategy using advance consent'. The article concludes that 'early enrollment strategy with advance consent appears to be an acceptable approach among key stakeholders'.
Karlwish <i>et al</i> ²⁸	No opinion for or against the use of advance consent for research	The authors outline that 'advance informed consent means, that at a time before enrollment, an investigator seeks the consent of a competent person who is a potential subject of a research trial.(...)Like advance directives for clinical care such as living wills, regulations could endorse advance directives for research'. They then explain that 'a moral conflict can occur when an advance directive conflicts with substituted judgement or best interests principles' and that 'there are the practical limits, including that an advance directive cannot address every circumstance a potential subject faces and that many people do not execute them'.
McGehrin <i>et al</i> ²⁵	In favour of use of advance consent for research	The article states that 'one solution to preserving patient autonomy in acute stroke care is the advent of a stroke advance directive. An advance directive for acute stroke therapy was created at the University of California, San Diego (UCSD) in 2015 titled COAST (Coordinating Options for Acute Stroke Therapy). This 4-page form allows patients to document their preferences regarding acute stroke treatment interventions, as well as participation in clinical stroke trials, in a nonurgent setting and in advance of a potential stroke'.

ED, emergency department; IM, intramuscular; RCT, randomised controlled trial.

did not describe what information would be recorded regarding preferences for involvement in future stroke trials, nor did it detail how this information would be used for future enrolment in research studies.

DISCUSSION

Our scoping review maps the existing literature on the use of advance consent for enrolling participants into RCTs for emergency conditions. The results of our review demonstrate that there has been minimal exploration of the use of advance consent for enrolment in RCTs for emergency conditions. We could only identify one study that had attempted the use of advance consent in an adult population²⁹ and one study in which opinions about advance consent were elicited.²⁷ No studies had endeavoured to use advance consent for enrolment into research in emergency neurological conditions.

The limited literature on the use of advance consent may suggest that there are concerns surrounding feasibility, but we believe the issues raised by Cole *et al* and Biros *et al* are potentially remediable.^{26 29} For example, selecting conditions for which a clearly defined at-risk population exists, such as acute ischaemic stroke, would likely enhance feasibility. A recent assessment of local data at a tertiary care centre in Ottawa (Ontario, Canada) also supports the feasibility of advance consent in selected

at-risk populations, in this case neurological emergencies. The data established that 5%–7% of patients seen in the stroke prevention clinic with minor stroke or transient ischaemic attack presented to the ED with an acute stroke within 1 year of their clinic appointment. These data reflect a potential 100–150 candidates annually who could be consented in clinic using advance consent methods for RCTs pertaining to acute ischaemic strokes in the ED.³⁰ Moreover, an electronic medical record could be used to document decisions about advance consent in such a way that it is obvious on presentation to the ED. Because the study by Cole *et al* failed to enrol a patient using advance consent, they conclude that the approach is not feasible; we believe it is important to note that they struggled to enrol patients into their study by any means and that this is unlikely owing simply to the use of advance consent. Biros *et al* raise an important concern about patients being unable to consider consent carefully when potential enrolment is remote. However, Corneli *et al* directly addressed this issue in their survey and found that nearly all patient and caregiver respondents were not concerned about a patient's ability to understand consent information for a potential future trial.

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 (eg, a patient who consents to participate in any acute stroke trial) as a stand-in for specific informed consent (eg, a specific stroke trial). Second, how would advance consent from an incapable patient be prioritised 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 authorised 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.

The strengths of our review are that we prospectively registered our study, used a thorough protocol, and systematically searched, screened and summarised the literature on advance consent for research in acute care RCTs. We also employed broad inclusion criteria, which did not restrict the type of included publications in our review. This ensured that we were able to survey all of the available literature on our topic of interest. Our study was not without limitations. Despite our comprehensive search strategy, there was little literature on this topic, and due to the heterogeneity of study types ultimately included in our analysis, there is inherent risk of bias. Because we conducted a scoping review, we did not perform a specific risk of bias assessment of each individual manuscript identified and data synthesis was not performed.

Ultimately, we suspect that advance consent could offer several important advantages over existing trial recruitment methods. Most importantly, advance consent could create a more ethical system for trial enrolment by ensuring that patients' wishes to be enrolled or not enrolled into trials are respected even if they cannot express them at the time of a medical emergency. Advance consent could reduce the time required to enrol willing patients into trials of time-sensitive treatments, potentially leading to better individual outcomes. It could render research findings more generalisable by removing biases against more severely affected patients or non-accompanied patients. It could even allow RCTs to be completed more quickly, as enrolment rates may be enhanced, leading to a more rapid determination of

research results. Future studies could aim to assess the acceptability of advance consent to potential participants, along with the feasibility of enrolling potential research participants using this method of consent.

In summary, our scoping review demonstrates that there has been minimal exploration on the use of advance consent for enrolment in RCTs for emergency conditions, and significant gaps in the literature remain. Furthermore, there have been no studies assessing the use of advance consent for enrolment in RCTs involving neurological emergencies. Patients and caregivers appear open to participate in advance consent for emergency conditions.

Contributors All authors made substantial contributions to the manuscript. NN, BD, JP, DD and MS designed the research question. NN, BD and MS designed the eligibility criteria and the screening strategy. BD, DD and MS designed the search strategy. NN, RL, BD and MS came up with the data extraction items and developed the data synthesis strategy. All authors contributed to analysis, drafting and editing and provided final approval. MS acts as the guarantor for the study.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Naomi Niznick <http://orcid.org/0000-0003-0935-9135>

Ronda Lun <http://orcid.org/0000-0001-8455-8201>

Brian Dewar <http://orcid.org/0000-0002-9222-5420>

REFERENCES

- 1 Dickert NW, Brown J, Cairns CB, *et al*. Confronting ethical and regulatory challenges of emergency care research with conscious patients. *Ann Emerg Med* 2016;67:538–45.
- 2 Mangset M, Førde R, Nessa J, *et al*. I don't like that, it's tricking people too much... acute informed consent to participation in a trial of thrombolysis for stroke. *J Med Ethics* 2008;34:751–6.
- 3 Wendler D, Dickert NW, Silbergleit R, *et al*. Targeted consent for research on standard of care interventions in the emergency setting. *Crit Care Med* 2017;45:e105–10.
- 4 Goyal M, Demchuk AM, Menon BK, *et al*. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* 2015;372:1019–30.

- 5 Shamy MCF, Dewar B, Chevrier S, *et al.* Deferral of consent in acute stroke trials. *Stroke* 2019;50:1017–20.
- 6 Burns KEA, Zubrinich C, Marshall J, *et al.* The “ consent to research ” paradigm in critical care: challenges and potential solutions. *Intensive Care Med* 2009;35:1655–8.
- 7 61 21 CFR part 50. protection of human subjects: informed consent and waiver of consent requirements in certain emergency research; final rules. *Food and Drug Administration; Federal Register* 1996;51498–2332.
- 8 World Medical Association. The declaration of helsinki: ethical principles for medical research involving human subjects 2008. n.d. Available: <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>
- 9 Beauchamp TL, Fost N, Robertson JA. The ambiguities of “deferred consent.” *IRB* 1980;2:6–9.
- 10 van Belle G, Mentzelopoulos SD, Aufderheide T, *et al.* International variation in policies and practices related to informed consent in acute cardiovascular research: results from a 44 country survey. *Resuscitation* 2015;91:76–83.
- 11 Bravo G, Dubois M-F, Wildeman SM, *et al.* Research with decisionally incapacitated older adults: practices of canadian research ethics boards. *IRB* 2010;32:1–8.
- 12 Largent EA, Wendler D, Emanuel E, *et al.* Is emergency research without initial consent justified?: the consent substitute model. *Arch Intern Med* 2010;170:668–74.
- 13 Saks ER, Dunn LB, Wimer J, *et al.* Proxy consent to research: the legal landscape. *Yale J Health Policy Law Ethics* 2008;8:37–92.
- 14 Government of Canada. Tri-council policy statement on ethical conduct for research involving human. *Section* 2016;3:11.
- 15 Sachs GA. Advance consent for dementia research. *Alzheimer Dis Assoc Disord* 1994;8(Suppl. 4):19–27.
- 16 Buller T. Advance consent, critical interests and dementia research. *J Med Ethics* 2015;41:701–7.
- 17 Stocking CB, Hougham GW, Danner DD, *et al.* Speaking of research advance directives: planning for future research participation. *Neurology* 2006;66:1361–6.
- 18 Pierce R. A changing landscape for advance directives in dementia research. *Soc Sci Med* 2010;70:623–30.
- 19 Niznick N, Lun R, Dewar B, *et al.* Advanced consent for participation in acute care randomised control trials: protocol for a scoping review. *BMJ Open* 2020;10:e039172.
- 20 Tricco AC, Lillie E, Zarin W, *et al.* PRISMA extension for scoping reviews (PRISMA-scr): checklist and explanation. *Ann Intern Med* 2018;169:467–73.
- 21 Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *International Journal of Social Research Methodology* 2005;8:19–32.
- 22 Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. *Implement Sci* 2010;5:69.
- 23 Covidence systematic review software. Veritas health innovation melbourne, australia. n.d. Available: www.covidence.org
- 24 Backlar P. A choice of one's own research advance directives: anticipatory planning for research subjects with fluctuating or prospective decisionmaking impairments. *Account Res* 1999;7:117–28.
- 25 McGehrin K, Spokoyny I, Meyer BC, *et al.* The coast stroke advance directive: a novel approach to preserving patient autonomy. *Neurol Clin Pract* 2018;8:521–6.
- 26 Biros MH, Lewis RJ, Olson CM, *et al.* Informed consent in emergency research. *JAMA* 1995;273:1283.
- 27 Corneli A, Perry B, Collyar D, *et al.* Assessment of the perceived acceptability of an early enrollment strategy using advance consent in health care-associated pneumonia. *JAMA Netw Open* 2018;1:e185816.
- 28 Karlawish JH, Sachs GA. Research on the cognitively impaired: lessons and warnings from the emergency research debate. *J Am Geriatr Soc* 1997;45:474–81.
- 29 Cole JB, Klein LR, Mullinax SZ, *et al.* Study enrollment when “ preconsent ” is utilized for a randomized clinical trial of two treatments for acute agitation in the emergency department. *Acad Emerg Med* 2019;26:559–66.
- 30 Shamy M, Dewar B, Niznick N, *et al.* Advanced consent for acute stroke trials. *Lancet Neurol* 2021;20:S1474-4422(21)00029-6:170..

SUPPLEMENTARY MATERIAL

Supplementary Material Legend

Supplementary Table 1: Search strategies

Supplementary Table 2: Data charting form

Supplementary Table 1. Search strategy

Database	Search terms	Results
Embase Classic + Embase (1947 – February 10, 2020)	1. ((advance* or prior or prospective*) adj3 consent).tw.	2844
	2. (preconsent or pre-consent).tw.	43
	3. Advance Directives/ and Informed Consent/	1361
	4. 1 or 2 or 3	4206
	5. incapacitated.tw.	1984
	6. *heart infarction/	112881
	7. (cardiac arrest or heart arrest or heart attack or asystole or cardiopulmonary arrest*).tw.	67289
	8. (myocardial infarct* or myocardial isch*).tw.	318778
	9. (cardiac death or heart death or arrhythmic death).tw.	41772
	10. *dementia/	54639
	11. (dementia or alzheimer*).tw.	292062
	12. *cerebrovascular accident/	78550
	13. (stroke or intracerebral h?emorrhage).tw.	385677
	14. *brain hemorrhage/	33439
	15. *epileptic state/	10938
	16. (epilepsy or status epilepticus).tw.	165346
	17. *subarachnoid hemorrhage/	21563
	18. subarachnoid h?emorrhage.tw.	32523
	19. exp *injury/	1111912
	20. ((neurolog* or brain) adj3 (emergenc* or injur* or trauma*)).tw. (114863
	21. emergency care/	44041
	22. (emergency department* or emergency treatment* or emergency setting* or emergency situation*).tw.	149499
	23. emergency treatment/	17365
	24. emergenc*.ti.	142870
	25. *human experiment/	5564
	26. *"clinical trial (topic)"/	10702
	27. *emergency medicine/	27031
	28. *emergency ward/	30666
	29. *clinical research/ or *medical research/	83362
	30. or/5-29	2684505
	31. 4 and 30	629
Ovid MEDLINE(R) ALL (1946 – February 10, 2020)	1. ((advance* or prior or prospective*) adj3 consent).tw.	1159
	2. (preconsent or pre-consent).tw,kf.	25
	3. Advance Directives/ and Informed Consent/	633
	4. or/1-3	1786
	5. incapacitated.tw.	1254
	6. Myocardial Infarction/	163865
	7. (cardiac arrest or heart arrest or heart attack or asystole or cardiopulmonary arrest*).tw.	41358
	8. (myocardial infarct* or myocardial isch*).tw,kw.	218769
	9. (cardiac death or heart death or arrhythmic death).tw,kw.	23707
	10. Dementia/ or (dementia or alzheimer*).tw,kf.	220951
	11. exp Stroke/ or (stroke or intracerebral h?emorrhage).tw,kf.	279104
	12. exp Cerebral Hemorrhage/ or Status Epilepticus/	41146

	13. (epilepsy or status epilepticus).tw,kw.	109855
	14. exp Subarachnoid Hemorrhage/ or subarachnoid h?emorrhage.tw,kw.	29908
	15. exp "Wounds and Injuries"/	889722
	16. ((neurolog* or brain) adj3 (emergenc* or injur* or trauma*)).tw.	79721
	17. Emergency Service, Hospital/	66069
	18. Emergencies/ or Emergency Medicine/ or exp Emergency Treatment/ (164845
	19. (emergency department* or emergency treatment* or emergency setting* or emergency situation*).tw.	97671
	20. emergenc*.ti.	109009
	21. exp Human Experimentation/	12414
	22. Clinical Trials as Topic/ or Biomedical Research/	257452
	23. or/5-22	2295131
	24. 4 and 23	454
EBM Review – Cochrane Central Register of Controlled Trials (February 10, 2020)	1. ((advance* or prior or prospective*) adj3 consent).tw.	3608
	2. (preconsent or pre-consent).tw.	15
	3. Advance Directives/ and Informed Consent/	1
	4. or/1-3	3621
	5. incapacitated.tw.	100
	6. Myocardial Infarction/	10416
	7. (cardiac arrest or heart arrest or heart attack or asystole or cardiopulmonary arrest*).tw. (4770
	8. (myocardial infarct* or myocardial isch*).tw.	30889
	9. (cardiac death or heart death or arrhythmic death).tw.	3461
	10. Dementia/ or (dementia or alzheimer*).tw.	18563
	11. exp Stroke/ or (stroke or intracerebral h?emorrhage).tw.	52260
	12. exp Cerebral Hemorrhage/ or Status Epilepticus/	1030
	13. (epilepsy or status epilepticus).tw,kw.	6807
	14. exp Subarachnoid Hemorrhage/ or subarachnoid h?emorrhage.tw,kw.	1950
	15. exp "Wounds and Injuries"/	22743
	16. ((neurolog* or brain) adj3 (emergenc* or injur* or trauma*)).tw.	6550
	17. Emergency Service, Hospital/	2083
	18. Emergencies/ or Emergency Medicine/ or exp Emergency Treatment/	6536
	19. (emergency department* or emergency treatment* or emergency setting* or emergency situation*).tw.	11275
	20. emergenc*.ti.	7206
	21. exp Human Experimentation/	133
	22. Clinical Trials as Topic/ or Biomedical Research/	33365
	23. or/5-22	180502
	24. 4 and 23	309
	25. (EUCTR* or IRCT* or ISRCT* or CTRI* or JPRN* or DRKS* or CHICTR* or NCT* or ACTRN*).au.	300851
	26. 24 not 25	106
Web of Science (February 10, 2020)	TS=(preconsent or pre-consent)	33
	TS=((advance* or prior or prospective*) NEAR/3 consent)	1870

#2 OR #1	1899
TS=incapacitated	3429
TS=("cardiac arrest" or "heart arrest" or "heart attack" or asystole or "cardiopulmonary arrest*")	49571
TS=("myocardial infarct*" or "myocardial isch*").	326927
TS=("cardiac death" or "heart death" or "arrhythmic death")	31798
I	
TS=(dementia or alzheimer*)	319597
TS=(stroke or "intracerebral h?emorrhage")	345906
TS=(epilepsy or "status epilepticus")	149826
TS="subarachnoid h?emorrhage*"	3980
TS=((neurolog* or brain) NEAR/3 (emergenc* or injur* or trauma*))	118137
TS= ("emergency department*" or "emergency treatment*" or "emergency setting*" or "emergency situation*")	107877
TI=emergenc*	153160
TS=clinical research	346041
TS="human experiment*"	2638
I	
#16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4	1747826
#17 AND #3	343

Supplementary Table 2. Data charting form

SECTION	DATA ITEM	EXTRACTED DATA
Study identification		
	Paper number	
	Journal - Title	
	Article - Title	
	Author last name	
	Type of author (MD/PhD/Other)	MD PhD Other
	Publication date (Year)	
	Country of Origin	Canada United States United Kingdom Other country in North or South America Other country in Europe Other country in Asia Other country in Africa
Study characteristics & methodology		
<i>Medical condition</i>	What is the condition?	Ischemic Stroke ICH Seizure Cardiac Respiratory Psychiatric None [no mentioned condition] Other
	Is the condition neurological?	Yes No
<i>Paper characteristics</i>	Type of research paper	RCT Cohort Case-Control Survey Interview Commentary Philosophical argument Historical review Other
	If clinical study, was Advance consent used?	Yes No Not applicable
Results		
	Author disposition	In favour of advance consent Against advance consent

		No opinion mentioned
	Specific statements	Extract any paragraph of text where advance consent is discussed

ICH = intracerebral hemorrhage; RCT = randomized control trial