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ADVANCE CONSENT FOR PARTICIPATION IN RANDOMIZED CONTROLLED TRIALS FOR EMERGENCY CONDITIONS: A SCOPING REVIEW

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ADVANCE CONSENT FOR PARTICIPATION IN RANDOMIZED CONTROLLED TRIALS FOR EMERGENCY CONDITIONS: A SCOPING REVIEW

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ABSTRACT

Objectives: Advance consent is a recognized 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 enrollment in randomized control trials (RCTs) for emergency conditions.

Design: Scoping review designed in accordance with the PRISMA-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 February 10, 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 was extracted directly from included papers using a standardized data charting form. We produced a narrative review including article type and authors' dispositions towards advance consent.

Results: Our search yielded 1,039 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 enroll participants into a clinical trial for an emergency condition.

Conclusion: Our review demonstrates that there has been minimal exploration of advance consent for enrollment 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.[1]

STRENGTHS & LIMITATIONS

- This scoping review outlines a novel approach to obtaining consent for enrollment in randomized control trials.

- We systemically summarized 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.

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 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.[2-4] These challenges have been increasingly recognized in the design of trials for emergency neurological conditions such as acute ischemic stroke and intracerebral hemorrhage, where patients are almost universally incapable of providing consent and enrollment decisions need to happen on a scale of minutes.[5, 6] 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 randomized controlled trials (RCTs) with consent from a substitute decision maker (SDM).[7] Other potential methods of enrollment 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.[8-10] Availability and acceptability of approaches to consent may vary depending on legal or cultural factors.[7, 11, 12]

Advance consent for enrollment 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.[13, 14] 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 advanced consent; the Canadian TCPS2 statement explicitly requires researchers and authorized parties to "be guided by these directives".[15] Historically, advance consent has mainly been used for research in predictably progressive diseases, such as Alzheimer's dementia.[16-19] 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 recognized risk factors. For example, 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 ischemic 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 enrollment 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.[1] A detailed protocol of the study design and methods was developed, and published a priori.[1] This scoping review was designed in accordance with the PRISMA-Extension for Scoping Reviews guidelines.[20] It was conducted using the framework of Arksey and O'Malley, and further defined by Levac.[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 February 10, 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 Supplementary 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. 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).

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	(a) Non-emergency conditions, such as dementia, and non-emergent treatment (b) Pregnancy
Topic of interest	Advance consent for participation in RCTs	(a) Other forms of consent such as deferred consent or waiver of consent (b) Advance care planning in areas other than research such as medical care, treatment, and advance consent for end-of-life care

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, 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, 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 (NN, RL) onto a standardized data charting form (Supplementary 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, other), and publication country of

origin. Data on the paper characteristics, methodology, medical condition of interest, and method of employing advance consent for research was 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 enroll 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 synthesized 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 1,532 studies. With duplicates removed, 1,039 titles and abstracts were screened, and 29 full-text articles were reviewed. No additional publications were including after reviewing the reference lists. Six articles met inclusion criteria (Figure 1).

Article characteristics

The six articles were published from 1995 to 2019. All of the articles were from the United States. 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 statement,[26] one consisted of semi-structured

interviews,[27] one was a historical review,[28] and one was a cohort study.[29] Specific conditions 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 semi-structured interviews to determine stakeholders' perceptions of the use of advance consent for enrollment 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 stroke patients, but did not elaborate on advance consent specifically.[25] Only one study reported using advance consent to enroll participants into a clinical trial (Table 2).[29]

Table 2. Characteristics of included articles

Author	Year	Country	No.	Type of article	Condition	Description of use of advance consent
Backlar	1999	United States	369	Commentary	Psychiatric - Schizophrenia	Author discusses the theoretical use of research advance directives
Biros et al.	1995	United States	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 United States.
Cole et al.	2019	United States	1165	Cohort	Psychiatric - Agitation	Authors employ the use advance consent for enrollment in an RCT. Observational cohort study of patients screened and consented in advance for potential future enrollment in a randomized trial examining treatments for acute agitation in the ED.
Corneli et al.	2018	United States	1095	Interview	Respiratory - Pneumonia	Authors interview stakeholders to determine the perceived acceptability of the use advance consent for enrollment in a theoretical RCT.
Karlawish et al.	1997	United States	340	Historical review	No specific conditioned mentioned: "Emergency medicine"	Authors explain research advance directives and discuss the ethics and regulations in the United States concerning the use of advance consent for research on emergency conditions.

McGehrin et al.	2018	United States	811	Commentary	Neurologic - Ischemic stroke	Authors outline the use of a standardized 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.

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 patients (Corneli *et al.*) and that it enhances patient autonomy (Backlar, McGehrin *et al.*).[24, 25, 27] The arguments against advance consent were that it was not feasible (Cole *et al.*, Biros *et al.*), that participants would not be adequately informed (Biros *et al.*) and that it would not protect patients from the risks of participation in RCTs (Biros *et al.*).[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 United States (Karlawish *et al.)*.[28]

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

Author	Author's disposition	Description of supporting evidence
Backlar	*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 et al.	*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 advanced consent at hospital admission for a potential future research protocol, the authors argue that pre-consent "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 advanced 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 et al.	*Against* use of advance consent for research	The authors screened 1,461 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 >1,400 patients and obtaining preconsent in 43 patients", not a single patient was enrolled using preconsent methods. Only 2 patients were enrolled into the study, and the study was terminated 1 month after enrollment of the first patient due to loss of funding. The article concludes that the utilization of preconsent in their study was "found to be infeasible".
Corneli et al.	*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".
Karlawish et al.	*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 judgment 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 et al.	*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."

Experiences with advance consent

Corneli *et al* was the only study to report the results of empirical research, in that they conducted semi-structured 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 in enrollment – in this case, pneumonia. The authors therefore concluded that an early enrollment strategy with advance consent would be acceptable.

Cole *et al* presented the sole experience using advance consent for study enrollment.[29] The authors conducted an observational cohort study of psychiatric participants pre-consented for an RCT examining treatments for acute agitation in the Emergency department (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 authorized 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 enrollment.

Advance consent and emergency neurologic conditions

The article by McGehrin *et al.* was the only paper that specifically focused on neurologic conditions. McGehrin *et al* proposed a 4-page advance directive document they call 'Coordinating Options for Acute Stroke Therapy (COAST)', which is designed to allow patients to document their preferences regarding acute stroke treatment, including participation in future clinical stroke trials.[25] The article 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 utilized 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 enrollment in RCTs for emergency conditions. We could only identify one study that had attempted the use of advance consent in an adult population,[29] and one study in which opinions about advance consent were

elicited.[27] No studies had endeavoured to use advance consent for enrollment 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 ischemic 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 neurologic 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 emergency department with an acute stroke within 1 year of their clinic appointment. This data reflects a potential 100–150 candidates annually who could be consented in clinic using advance consent methods for RCTs pertaining to acute ischemic strokes in the emergency department. ("Advance consent for acute stroke trials", The Lancet Neurology, 2021). Moreover, an electronic medical record could be used to document decisions about advance consent in such a way that it is obvious upon presentation to the emergency department. Because the study by Cole *et al.* failed to enroll a patient using advance consent, they conclude that the approach is not feasible; we believe it is important to note that they struggled to enroll 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 enrollment 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.

The strengths of our review are that we prospectively registered our study, utilized a thorough protocol, and systematically searched, screened and summarized 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 enrollment 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 enroll willing patients into trials of time-sensitive treatments, potentially leading to better individual outcomes. It could render research findings more generalizable by removing biases against more severely affected patients or non-accompanied patients. It could even allow RCTs to be completed more quickly, as enrollment rates may be enhanced leading to the 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 advanced consent for enrollment 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 enrollment in RCTs involving neurologic emergencies. Patients are caregivers appear open to participate in advance consent for emergency conditions.

DECLARATIONS

Ethics approval and consent to participate

Not applicable.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

All authors made substantial contributions to the manuscript.

NN/BD/JP/DD/MS designed the research question, NN/BD/MS designed the eligibility criteria, BD/DD/MS designed the search strategy, NN/BD/MS designed the screening strategy, NN/RL/BD/MS came up with the data extraction items and NN/RL/BD/MS developed the data synthesis strategy. All authors contributed to analysis, drafting, editing and provided final approval.

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Figure Legend

Figure 1: Preferred reporting items for Systematic Reviews and Meta Analyses Flow Diagram

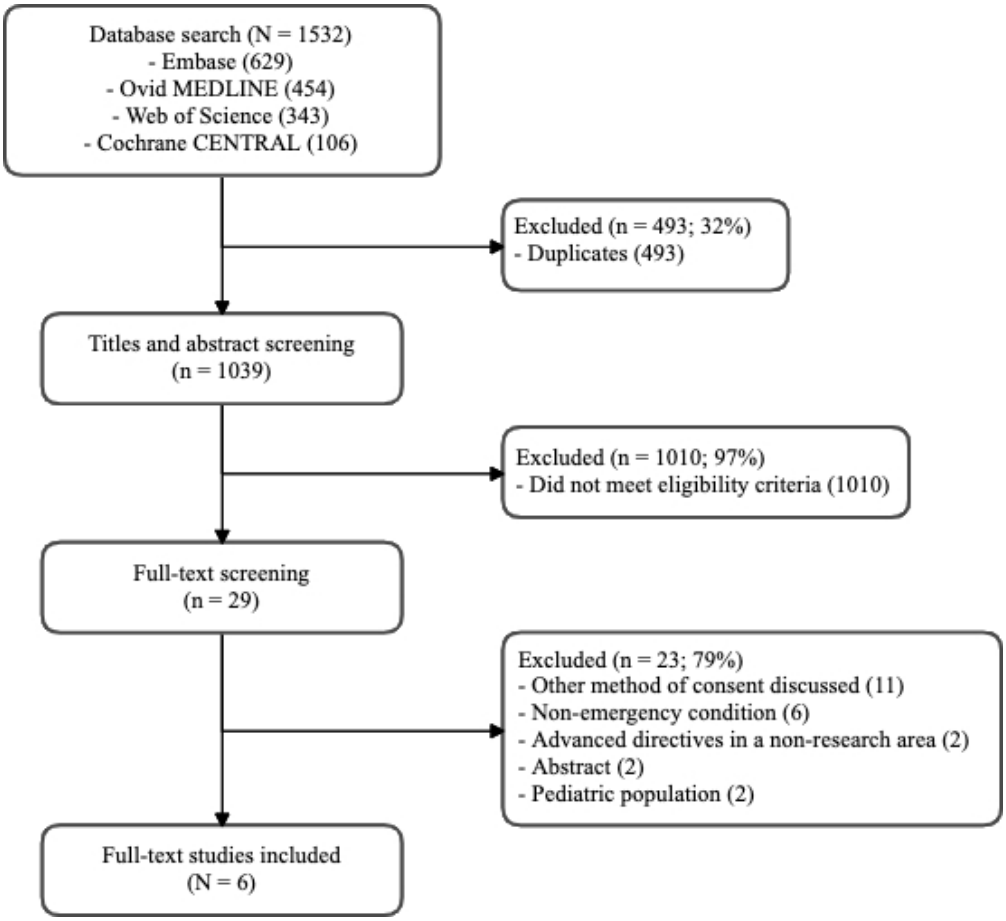

Figure 1: Preferred reporting items for Systematic Reviews and Meta Analyses Flow Diagram

195x178mm (72 x 72 DPI)

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		
Medical condition	What is the condition?	Ischemic Stroke ICH Seizure Cardiac Respiratory Psychiatric None [no mentioned condition] Other
	Is the condition neurological?	Yes No
Paper characteristics	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

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	
Limitations	20	Discuss the limitations of the scoping review process.	
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.
* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).
‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

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ADVANCE CONSENT FOR PARTICIPATION IN RANDOMIZED CONTROLLED TRIALS FOR EMERGENCY CONDITIONS: A SCOPING REVIEW

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ADVANCE CONSENT FOR PARTICIPATION IN RANDOMIZED CONTROLLED TRIALS FOR EMERGENCY CONDITIONS: A SCOPING REVIEW

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Keywords: Consent; advance directives; research ethics; emergencies; scoping review.

ABSTRACT

Objectives: Advance consent is a recognized 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 enrollment in randomized control trials (RCTs) for emergency conditions.

Design: Scoping review designed in accordance with the PRISMA-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 February 10, 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 was extracted directly from included papers using a standardized data charting form. We produced a narrative review including article type and authors' dispositions towards advance consent.

Results: Our search yielded 1,039 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 enroll participants into a clinical trial for an emergency condition.

Conclusion: Our review demonstrates that there has been minimal exploration of advance consent for enrollment 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.

STRENGTHS & LIMITATIONS

- This scoping review outlines a novel approach to obtaining consent for enrollment in randomized control trials.

- We systemically summarized 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.

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 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 recognized in the design of trials for emergency neurological conditions such as acute ischemic stroke and intracerebral hemorrhage, where patients are almost universally incapable of providing consent and enrollment 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 randomized controlled trials (RCTs) with consent from a substitute decision maker (SDM).[6] Other potential methods of enrollment 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 enrollment 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 advanced consent; the Canadian TCPS2 statement explicitly requires researchers and authorized 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 recognized risk factors. For example, 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 ischemic 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 enrollment 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 PRISMA-Extension for Scoping Reviews guidelines.[20] It was conducted using the framework of Arksey and O'Malley, and further defined by Levac.[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 February 10, 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 Supplementary 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 hospitalized patients and in the emergency department. 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).

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	(a) Non-emergency conditions, such as dementia, and non-emergent treatment (b) Pregnancy
Topic of interest	Advance consent for participation in RCTs	(a) Other forms of consent such as deferred consent or waiver of consent (b) Advance care planning in areas other than research such as medical care, treatment, and advance consent for end-of-life care

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, 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, 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 (NN, RL) onto a standardized data charting form (Supplementary 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, other), and publication country of origin. Data on the paper characteristics, methodology, medical condition of interest, and method of employing advance consent for research was 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 enroll 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 synthesized 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 1,532 studies. With duplicates removed, 1,039 titles and abstracts were screened, and 29 full-text articles were reviewed. No additional publications were including after reviewing the reference lists. Six articles met inclusion criteria (Figure 1).

Article characteristics

The six articles were published from 1995 to 2019. All of the articles were from the United States. 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 statement,[26] one consisted of semi-structured interviews,[27] one was a historical review,[28] and one was a cohort study.[29] Specific conditions 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 semi-structured interviews to determine stakeholders' perceptions of the use of advance consent for enrollment 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 stroke patients, but did not elaborate on advance consent specifically.[25] Only one study reported using advance consent to enroll participants into a clinical trial (Table 2).[29]

Table 2. Characteristics of included articles

Author	Year	Country	No.	Type of article	Condition	Description of use of advance consent
Backlar	1999	United States	369	Commentary	Psychiatric - Schizophrenia	Author discusses the theoretical use of research advance directives
Biros et al.	1995	United States	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 United States.
Cole et al.	2019	United States	1165	Cohort	Psychiatric - Agitation	Authors employ the use advance consent for enrollment in an RCT. Observational cohort study of patients screened and consented in advance for potential future enrollment in a randomized trial examining treatments for acute agitation in the ED.
Corneli et al.	2018	United States	1095	Interview	Respiratory - Pneumonia	Authors interview stakeholders to determine the perceived acceptability of the use advance consent for enrollment in a theoretical RCT.
Karlawish et al.	1997	United States	340	Historical review	No specific conditioned mentioned: "Emergency medicine"	Authors explain research advance directives and discuss the ethics and regulations in the United States concerning the use of advance consent for

						research on emergency conditions.
McGehrin et al.	2018	United States	811	Commentary	Neurologic - Ischemic stroke	Authors outline the use of a standardized 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.

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 patients (Corneli *et al.*) and that it enhances patient autonomy (Backlar, McGehrin *et al.*).[24, 25, 27] The arguments against advance consent were that it was not feasible (Cole *et al.*, Biros *et al.*), that participants would not be adequately informed (Biros *et al.*) and that it would not protect patients from the risks of participation in RCTs (Biros *et al.*).[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 United States (Karlawish *et al.)*.[28]

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

Author	Author's disposition	Description of supporting evidence
Backlar	*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 et al.	*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 advanced consent at hospital admission for a potential future research protocol, the authors argue that pre-consent "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 advanced 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 et al.	*Against* use of advance consent for research	The authors screened 1,461 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 >1,400 patients and obtaining preconsent in 43 patients", not a single patient was enrolled using preconsent methods. Only 2 patients were enrolled into the study, and the study was terminated 1 month after enrollment of the first patient due to loss of funding. The article concludes that the utilization of preconsent in their study was "found to be infeasible".
Corneli et al.	*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".
Karlawish et al.	*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 judgment 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 et al.	*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."

Experiences with advance consent

Corneli *et al* was the only study to report the results of empirical research, in that they conducted semi-structured 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 in enrollment – in this case, pneumonia. The authors therefore concluded that an early enrollment strategy with advance consent would be acceptable.

Cole *et al* presented the sole experience using advance consent for study enrollment.[29] The authors conducted an observational cohort study of psychiatric participants pre-consented for an RCT examining treatments for acute agitation in the Emergency department (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 authorized 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 enrollment.

Advance consent and emergency neurologic conditions

The article by McGehrin *et al.* was the only paper that specifically focused on neurologic conditions. McGehrin *et al* proposed a 4-page advance directive document they call 'Coordinating Options for Acute Stroke Therapy (COAST)', which is designed to allow patients to document their preferences regarding acute stroke treatment, including participation in future clinical stroke trials.[25] The article 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 utilized 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 enrollment in RCTs for emergency conditions. We could only identify one study that had attempted the use of advance consent in an adult population,[29] and one study in which opinions about advance consent were

elicited.[27] No studies had endeavoured to use advance consent for enrollment 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 ischemic 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 neurologic 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 emergency department with an acute stroke within 1 year of their clinic appointment. This data reflects a potential 100–150 candidates annually who could be consented in clinic using advance consent methods for RCTs pertaining to acute ischemic strokes in the emergency department. ("Advance consent for acute stroke trials", The Lancet Neurology, 2021). Moreover, an electronic medical record could be used to document decisions about advance consent in such a way that it is obvious upon presentation to the emergency department. Because the study by Cole *et al.* failed to enroll a patient using advance consent, they conclude that the approach is not feasible; we believe it is important to note that they struggled to enroll 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 enrollment 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 (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.

The strengths of our review are that we prospectively registered our study, utilized a thorough protocol, and systematically searched, screened and summarized 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 enrollment 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 enroll willing patients into trials of time-sensitive treatments, potentially leading to better individual outcomes. It could render research findings more generalizable by removing biases against more severely affected patients or non-accompanied patients. It could even allow RCTs to be completed more quickly, as enrollment

rates may be enhanced leading to the 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 advanced consent for enrollment 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 enrollment in RCTs involving neurologic emergencies. Patients are caregivers appear open to participate in advance consent for emergency conditions.

DECLARATIONS

Ethics approval and consent to participate

Not applicable.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

All authors made substantial contributions to the manuscript.

NN/BD/JP/DD/MS designed the research question, NN/BD/MS designed the eligibility criteria, BD/DD/MS designed the search strategy, NN/BD/MS designed the screening strategy, NN/RL/BD/MS came up with the data extraction items and NN/RL/BD/MS developed the data synthesis strategy. All authors contributed to analysis, drafting, editing and provided final approval.

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Figure Legend

Figure 1: Preferred reporting items for Systematic Reviews and Meta Analyses Flow Diagram

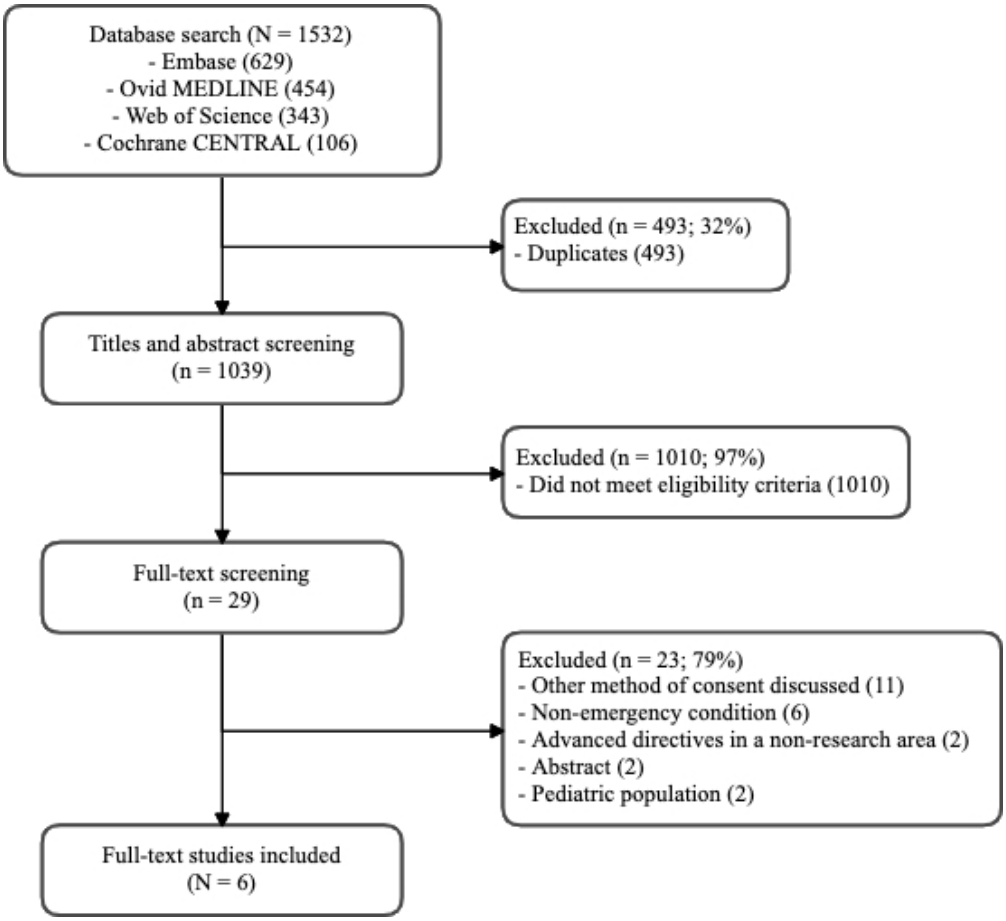

Figure 1: Preferred reporting items for Systematic Reviews and Meta Analyses Flow Diagram

195x178mm (72 x 72 DPI)

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		
Medical condition	What is the condition?	Ischemic Stroke ICH Seizure Cardiac Respiratory Psychiatric None [no mentioned condition] Other
	Is the condition neurological?	Yes No
Paper characteristics	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

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	
Limitations	20	Discuss the limitations of the scoping review process.	
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.
* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).
‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.