Eur J Cardiovasc Med. Author manuscript; available in PMC 2016 August 05.

Published in final edited form as:

Eur J Cardiovasc Med. 2016 April ; 4(1): 506–510. doi:10.5083/ejcm.20424884.147.

Refining the Enrolment Process in Emergency Medicine Research

Kate M Sahan[1,3], **Keith M Channon**[2,3], **Robin P Choudhury**[2,4], **Rajesh K Kharbanda**[2,3], **Regent Lee**[3], and **Mark Sheehan**[1,3]

[1]The Ethox Centre, Nuffield Department of Population Health, University of Oxford, Old Road Campus, Headington, Oxford OX3 7LF

[2]Radcliffe Department of Medicine University of Oxford, Level 6, West Wing, John Radcliffe Hospital, Headington, Oxford OX3 9DU

[3]NIHR Biomedical Research Centre, Oxford, The Joint Research Office, Block 60, The Churchill Hospital, Old Road, Headington, OX3 7LE

[4]Oxford Acute Vascular Imaging Centre, Division of Cardiovascular Medicine, University of Oxford

Abstract

Research in the emergency setting involving patients with acute clinical conditions is needed if there are to be advances in diagnosis and treatment. But research in these areas poses ethical and practical challenges. One of these is the general inability to obtain informed consent due to the patient's lack of mental capacity and insufficient time to contact legal representatives. Regulatory frameworks which allow this research to proceed with a consent 'waiver', provided patients lack mental capacity, miss important ethical subtleties. One of these is the varying nature of mental capacity among emergency medicine patients. Not only is their capacity variable and often unclear, but some patients are also likely to be able to engage with the researcher and the context to varying degrees. In this paper we describe the key elements of a novel enrolment process for emergency medicine research that refines the consent waiver and fully engages with the ethical rationale for consent and, in this context, its waiver. The process is verbal but independently documented during the 'emergent' stages of the research. It provides appropriate engagement with the patient, is context-sensitive and better addresses ethical subtleties. In line with regulation, full written consent for on-going participation in the research is obtained once the emergency is passed.

Keywords

informed consent; emergency medicine research; consent waiver; assent; mental capacity

Address for correspondence: Mrs Kate Sahan, The Ethox Centre, Nuffield Department of Population Health, University of Oxford, Old Road Campus, Headington, Oxford OX3 7LF. Phone 01865 287894. kate.sahan@ethox.ox.ac.uk.

Europe PMC Funders Author Manuscripts

Introduction

Research in the emergency setting involving patients with acute clinical conditions (including acute myocardial infarction (AMI) and stroke) is needed if there are to be advances in the diagnosis and treatments of those conditions. Despite its importance, research in these areas poses several ethical and practical challenges, not least in the area of patient consent. Fully informed consent, a central pillar of research ethics, cannot, for the most part, be obtained where the patient is in severe pain, incapacitated or under influence of powerful analgesic or sedative medication and where treatments need to be given very rapidly.

Regulatory frameworks have been developed to allow this research to proceed with a consent waiver but these frameworks miss important ethical subtleties. The process of enrolment described below applies to research involving patients who may be unable to provide written, fully informed consent because of an acute clinical condition and for whom there is no time to contact an approved representative. It represents a significant refinement of the simple consent waiver because it captures important ethical nuances without jeopardising the conduct of research.

Emergency Medicine Research

Well-known clinical trials such as ISIS (1, 2, 3), TROICA (4), CRASH (5,6), PAD (7) and PolyHeme (8) have all contributed significantly to acute patient care but they have also raised the profile of the ethical issues. Including UK patients in the international TROICA trial was initially prohibited by the UK Medicines for Human Use Act as this did not permit consent waivers. TROICA prompted an amendment to the Act (9, 10). In the US a range of trials and the generally recognised need to conduct research on resuscitation led to the production of the US Federal Regulations on the exception from informed consent in emergency research (11, 12).

There is a definite and continued need for research studies and clinical trials involving patients who are in the most acute clinical conditions in the emergency setting. For example, thrombolysis and emergency percutaneous coronary intervention (PCI) have yielded major benefits for patients compared with the pre-thrombolytic era. Further advances in the management of AMI require new experimental medicine studies and clinical trials, which are likely to be conducted within the context of immediate diagnosis and treatment by emergency PCI.

Ethics and regulation

There are two conventional principles of research ethics that conflict in the emergency medicine research context. First, it is ethically important that research in emergency medicine should proceed. As outlined above, without the knowledge that such research generates, emergency medicine clinicians are unable to discharge their obligations to continue to increase benefit and reduce potential harm to their patients. Second, it is usually considered imperative that participants give fully informed consent to be enrolled in the study (13, 14, 15).

Regulatory systems across the globe recognise that often both of these requirements cannot be satisfied in the emergency context. Patients require treatment urgently so there is little time for explanation, discussion and reflection. Patients may also be in extreme pain or shock, suffering from hemodynamic compromise, have already received opiates or be terrified thus compromising their capacity to make a considered decision. Both time and capacity are required for fully informed consent (16, 17). As a result the regulatory systems generally grant, under certain conditions (see Figure 1), an exemption from the requirement to obtain informed consent. Most importantly this exemption is based on the idea that informed consent requires capacity and that capacity will be lacking in many of the potential subjects of this research.

The new EU Clinical Trials Regulations No 536/2014 (18) with application from May 2016 accepts a “derogation” from written informed consent in certain emergency situations where it is not possible to obtain informed consent prior to an individual’s participation in a trial. In the UK the Medicines for Human Use (Clinical Trials) Amendment (No.2) (19) and the Mental Capacity Act (20) both allow research to be conducted on patients who lack capacity, with a ‘waiver’ of consent. In the US, the Federal Regulations allow an exception from the requirement to obtain informed consent (12, 21). In both cases, the authority to approve the use of the waiver is granted to Research Ethics Committees (RECs) subject to certain constraints (see Figure 1). More broadly, both the International Council for Harmonisation Good Clinical Practice Guidelines (ICH-GCP) and the Council for International Organizations of Medical Sciences (CIOMS) explicitly permit research on patients with acute clinical conditions subject to conditions very similar to those in place in the UK and the US (14, 15).

The problem

Research in the emergency context may need to be conducted even when the potential subject is incapable of giving their consent. For patients who are unconscious and when the relevant regulatory conditions (see Figure 1) are met, the requirement to obtain informed consent for these interventions can be waived. There will however be a group of patients who are conscious but will clearly lack capacity; others will remain on the edge of capacity; while still others will maintain the ability to make decisions. In ethical and legal terms, for this group of patients, the important issue is capacity: if the conscious patient has the capacity to decide, the regulations (and hence the consent waiver) do not apply. Not only is the capacity of patients in this group variable and often unclear, but because they are conscious they are also likely to be able to engage with the researcher and the context to varying degrees.

One option is to formally assess the capacity of potential research participants. This faces several serious difficulties. First, there are practical difficulties with requiring a suitably qualified individual always to be available for the formal determination of capacity. Second, such an assessment would take time where little or none may be available. Third, requiring a determination of capacity presumes that capacity is a binary concept. Capacity is usually taken to involve the ability to comprehend, retain and use information in making a decision (22). But clearly each person’s ability to satisfy these conditions will vary with context and

Europe PMC Funders Author Manuscripts

content and hence, that capacity will be a matter of degree (23). In considering issues of research ethics, there is a mismatch between the binary operation of the consent waiver and the extent to which individuals are able to comprehend what is happening to them. The problem here is that an individual may fail the 'capacity test' and yet be conscious enough to know that something different is happening about which they have not been informed, and / or to which they may not agree. By insisting on a strict determination of capacity this approach fails to take into account the realities of the situation and the nuances of the ethical relationships within them.

Refining the process

In what follows below we describe the key elements of an enrolment process for emergency medicine research that refines the consent waiver and addresses the challenges outlined above. These elements serve as an explanation of the flowchart of the process depicted in Figure 2. The key points of the process are summarised in text format (Figure 3).

1 Verbal consent

Overall, the emergency context provides a good justification for a consent process which is primarily verbal. As Roberts *et al* suggest there is evidence to suggest that requiring a detailed, written consent process in this context is potentially detrimental to the patient's health (17, 24).

What matters ethically for consent is that the autonomous (and so competent) person makes a voluntary decision having been given (and understanding) the relevant information. Importantly, there is nothing in this that requires consent to be written. It is an artefact of regulation and the need for evidence in this context. In the emergency context there is good reason to avoid unnecessary steps. However, it remains important, for the same reason that regulation is important, to have a record of the process that is independent of the researcher (25). Instead of requiring written consent, a verbal1 but independently documented process is one that is sensitive to the context of the research and the ethical issues surrounding consent.

2 Unconscious patients are enrolled on the consent waiver; Conscious patients go through a consent/assent process

The important ethical feature of the group of patients who are conscious but with unclear capacity is that they can, to varying degrees, engage with the researcher. There is a clear obligation on the part of both clinicians and researchers to engage with those patients who can, to the extent that the patient is able. The UK Mental Capacity Act acknowledges this obligation: "Nothing may be done to, or in relation to, [the patient] in the course of the research to which he appears to object (whether by showing signs of resistance or otherwise) except where what is being done is intended to protect him from harm or to reduce or prevent pain or discomfort" (26).

[1]A verbal process does not exclude non-verbal communication (gestures, expressions, head movements) which could also indicate consent or assent to study inclusion.

As a result, the process requires that the researcher responsible for the patient explains briefly and alongside whatever account of the clinical process is usually given, that research is being conducted and that they are eligible for enrolment. The study will, as far as possible, be discussed with the patient and the risks and benefits explained. Patients will be given the option to participate or not. In cases where capacity is unclear, any sign (verbal or non verbal) either to enrol in the study or not will be registered as assent or dissent. In cases of dissent the patient will not be entered into the study. This explanation and patients' responses do not stand in for a full consent process. It is verbal and truncated because of the emergency and it is delivered to all conscious patients to enable appropriate engagement. Those with capacity will understand and be able to consent in a truncated form while those with limited capacity will be given an opportunity to assent to (or dissent from) participation and so will be involved in the process to an appropriate extent. Judgement is required here to interpret any response on the part of the patient particularly in the negative. So while conscious patients are unlikely to be able to give full consent on this process they are given the opportunity to participate in the decision-making to the extent that they are able.

3 Patient Advocate

The Patient Advocate (PA) role is filled by a heath care professional present in the emergency room but independent of the research team, e.g. a clinical nurse or radiographer. The PA plays two important roles in the process: (i) to be an independent witness and to document that the process was undertaken appropriately and (ii) to provide an independent assessment of the patient's willingness or otherwise to participate in the research. The latter role requires the PA to witness the exchange between the researcher and the patient about the research study and to make a judgement in conjunction with the researcher about any affirmative or negative response by the patient. The patient advocate is not a surrogate for the patient or the legal representative of the patient but a trained independent observer who oversees the consent process and is in a position to interpret the patient's condition and responses to the researcher.

4 Consent for on-going participation

In line with regulatory requirements, full written consent for on-going participation in the research is obtained from the patient or their representative once the emergency is passed.

Conclusions

The process that we have outlined represents a nuanced approach to the research ethics around consent in the challenging context of emergency medicine research. The process suggested here does not involve a detailed, burdensome and time-consuming exercise that is often true of informed consent processes.

It balances the pressing need to conduct research in the emergency setting with an ethical approach that strives to inform and consult patients before their participation. It does not require simply withholding relevant information about research from participants and it does not require delays in life-saving interventions. Instead it is firmly embedded within the context of the consent waiver but represents an appropriate refinement of the regulations that

is better able to capture the ethical complexity of the context. It is context and patient sensitive. Most importantly, it is centred on a recognition that treating people well involves treating them honestly and engaging with them at a level appropriate to their specific circumstances.

Acknowledgements

Information on grants, contracts, and other forms of financial support:

Dr Mark Sheehan and Mrs Kate Sahan are funded by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre. Kate Sahan is supported by a Medical Sciences Graduate School Studentship from the UK Medical Research Council and the Nuffield Department of Population Health, University of Oxford

Abbreviations List

AMI	Acute Myocardial Infarction
CIOMS	Council for International Organizations of Medical Sciences
DHHS	United States Department of Health and Human Services
FDA	United States Food and Drug Administration
ICH-GCP	International Council for Harmonisation Good Clinical Practice Guidelines
PA	Independent Patient Advocate
PCI	Percutaneous Coronary Intervention
REC	Research Ethics Committee

References

(1). First International Study of Infarct Survival Collaborative Group. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. Lancet. 1986 Jul 12; 2(8498):57–66. [PubMed: 2873379]

(2). ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet. 1988 Aug 13; 2(8607):349–60. [PubMed: 2899772]

(3). ISIS-3 (Third International Study of Infarct Survival) Collaborative Group. ISIS-3: a randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. Lancet. 1992 Mar 28; 339(8796):753–70. [PubMed: 1347801]

(4). Böttiger BW, Arntz H-R, Chamberlain DA, et al. Thrombolysis during Resuscitation for Out-of-Hospital Cardiac Arrest. N Engl J Med. 2008; 359:2651–62. [PubMed: 19092151]

(5). CRASH trial collaborators. Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury— outcomes at 6 months. Lancet. 2005; 365:1957–59. [PubMed: 15936423]

(6). Roberts I, Shakur H, Afolabi A, et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet. 2011; 377(9771):1096–1101. 1101 e1091–1092. [PubMed: 21439633]

(7). The Public Access Defibrillation Trial Investigators. Public-Access Defibrillation and Survival after Out-of-Hospital Cardiac Arrest. N Engl J Med. 2004; 351:637–646. [PubMed: 15306665]

(8). Moore EE, Moore FA, Fabian TC, et al. Human polymerized hemoglobin for the treatment of hemorrhagic shock when blood is unavailable: the USA multicenter trial. J Am Coll Surg. 2009; 208(1):1–13. [PubMed: 19228496]

(9). Shakur H, Roberts I, Barnetson L, et al. Clinical trials in emergency situations. BMJ. 2007; 334(7586):165–166. DOI: 10.1136/bmj.39097.582130.80 [PubMed: 17255570]

(10). Warner, Lord; House of Lords. [Accessed 28 Jan 2016] HL Deb 18 January 2005, vol 668, Col WS24. 2005. Available at http://www.publications.parliament.uk/pa/ld200405/ldhansrd/vo050118/text/50118-53.htm#50118-53_head2

(11). Biros MH, Runge JW, Lewis RJ, Doherty JD. Emergency medicine and the development of the Food and Drug Administration's final rule on informed consent and waiver of informed consent in emergency research circumstances. Acad Emerg Med. 1998; 5(4):359–368. [PubMed: 9562204]

(12). U.S. Government Food and Drug Administration. [Accessed 29 January 2016] Exception from informed consent requirements for emergency research. 21 C.F.R. § 50.24. Available at http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm118995.htm

(13). Shuster E. Fifty Years Later: The Significance of the Nuremberg Code. N Engl J Med. 1997; 337(20):1436–40. [PubMed: 9358142]

(14). EMEA. European Medicines Agency. [Accessed 29 January 2016] ICH Topic E 6 (R1) Guideline for Good Clinical Practice. 1996. Available at http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf

(15). Council for International Organizations of Medical Sciences (CIOMS). [Accessed 29 January 2016] International Ethical Guidelines for Biomedical Research Involving Human Subjects. 2002. Available at http://www.cioms.ch/publications/layout_guide2002.pdf

(16). GMC. [Accessed 29 January 2016] Consent: patients and doctors making decisions together. 2008. Available at http://www.gmc-uk.org/Consent___English_1015.pdf_48903482.pdf

(17). Roberts I, Prieto-Merino D, Shakur H, Chalmers I, Nicholl J. Effect of consent rituals on mortality in emergency care research. Lancet. 2011 Mar 26; 377(9771):1071–2. [PubMed: 21439634]

(18). [Accessed 29 January 2016] REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Available at http://ec.europa.eu/health/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

(19). [Accessed 29 January 2016] Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations 2006. Statutory Instrument 2006 No 2984. Available at www.opsi.gov.uk/si/si2006/20062984.htm

(20). Mental Capacity Act 2005 (c.9) London: HMSO. Part 1, Section 32, subsections 8-9. Available at http://www.legislation.gov.uk/ukpga/2005/9/pdfs/ukpga_20050009_en.pdf [Accessed 29 January 2016]

(21). Offices of the Secretary, DHHS, FDA. Protection of Human Subjects: Informed Consent and Waiver of Informed Consent Requirements in Certain Emergency Circumstances: Final Rule. Fed Reg. Oct 2.1996 61:51497–531.

(22). Mental Capacity Act 2005 (c.9) London:HMSO. Part 1, Section 3, subsection 1. . Available at http://www.legislation.gov.uk/ukpga/2005/9/pdfs/ukpga_20050009_en.pdf [Accessed 29 January 2016]

(23). Buchanan, A.; Brock, D. Deciding for Others: the ethics of surrogate decision making. Cambridge: CUP; 1989. p. 18

(24). Kane I, Lindley R, Lewis S, Sandercock P. Impact of Stroke Syndrome and Stroke Severity on the Process of Consent in the Third International Stroke Trial. Cerebrovasc Dis. 2006; 21:348–52. [PubMed: 16490945]

(25). Coats TJ. Ethical and practical issues in trauma care research. Br J Surg. 2012; 99(Suppl 1):6–7. [PubMed: 22441848]

(26). Mental Capacity Act 2005 (c.9) London: HMSO. Part 1, Section 33, subsection 2(a). Available at http://www.legislation.gov.uk/ukpga/2005/9/pdfs/ukpga_20050009_en.pdf [Accessed 29 January 2016]

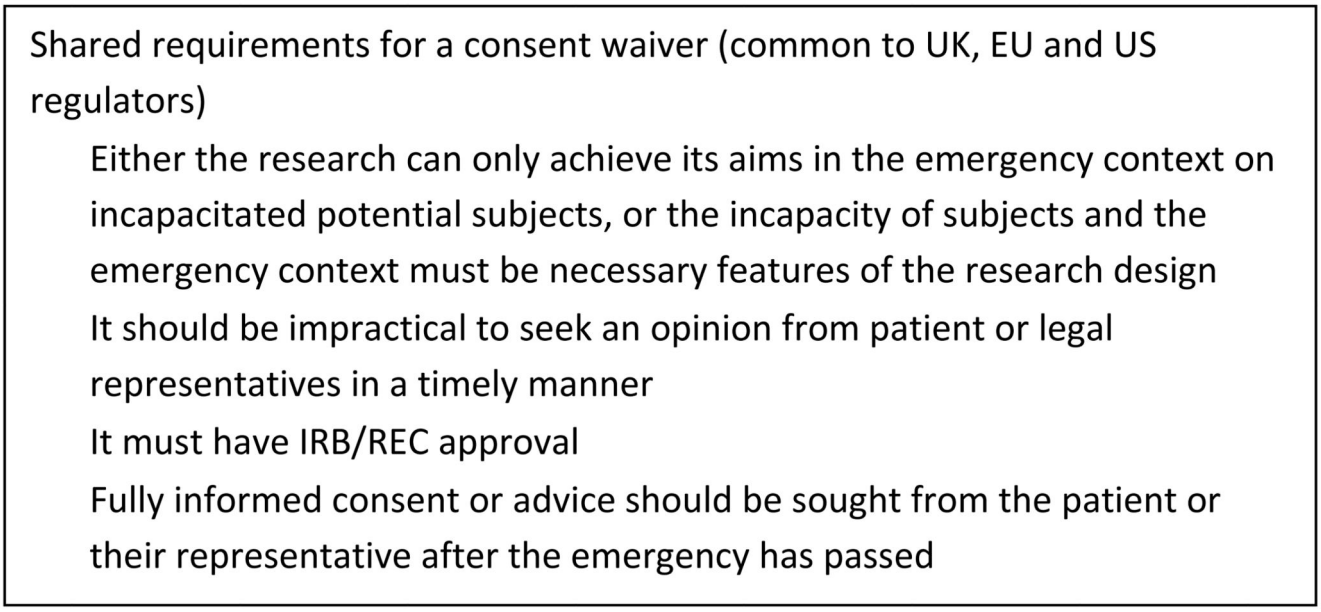

Figure 1. Shared requirements for a consent waiver.
The requirements listed are common to regulators from UK, EU and US

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

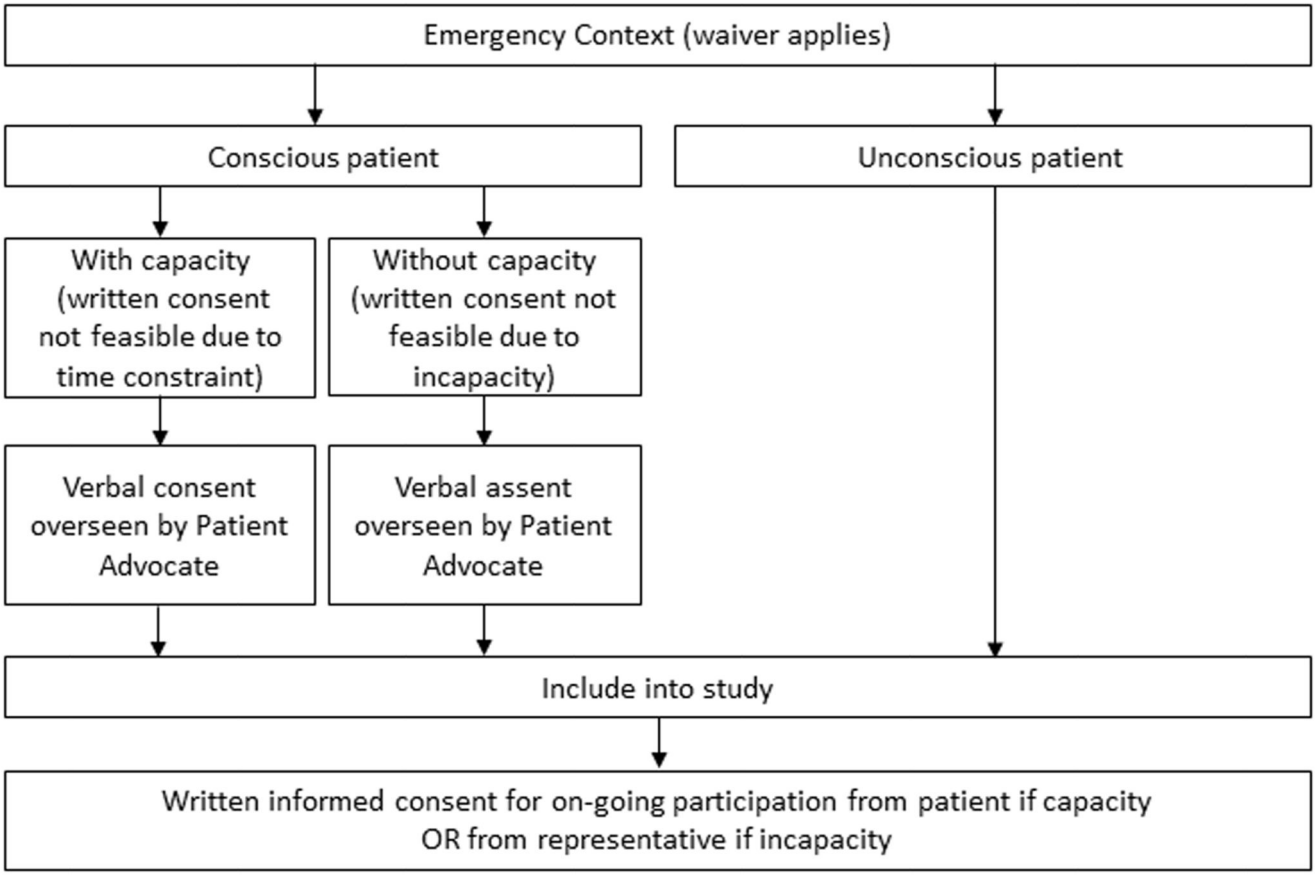

Figure 2. Refined enrolment process in emergency medicine research

Emergency admission patients eligible for inclusion in research follow one of three routes. An independent advocate oversees the process. Written consent is sought after the emergency is passed.

Europe PMC Funders Author Manuscripts

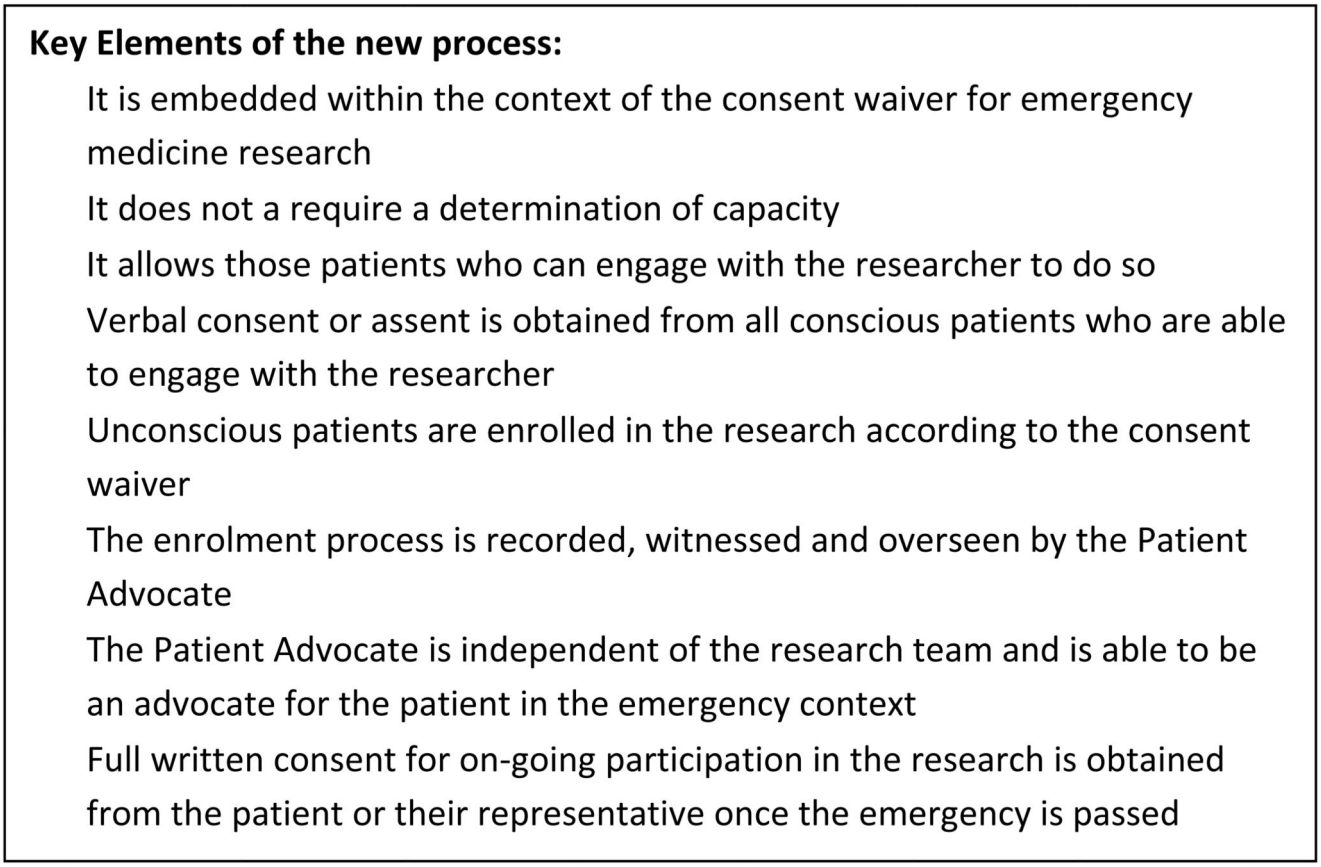

Figure 3. Key Elements of the new process
Key elements are described below