Citation for final published version:

Gobat, Nina Helene ORCID: https://orcid.org/0000-0002-1558-557X, Gal, Micaela ORCID: https://orcid.org/0000-0002-1326-190X, Francis, Nicholas Andrew, Hood, Kerenza, Watkins, Angela ORCID: https://orcid.org/0000-0002-1212-513X, Turner, Jill, Moore, Ronald, Webb, Steve A. R., Butler, Christopher Collett and Nichol, Alistair 2015. Key stakeholder perceptions about consent to participate in acute illness research: a rapid, systematic review to inform epi/pandemic research preparedness. Trials 16, 591. 10.1186/s13063-015-1110-6 file

Publishers page: http://dx.doi.org/10.1186/s13063-015-1110-6

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Key stakeholder perceptions about consent to participate in acute illness research: a rapid, systematic review to inform epi/pandemic research preparedness

Nina H. Gobat1*, Micaela Gal1, Nick A. Francis1, Kerenza Hood2, Angela Watkins1, Jill Turner3, Ronald Moore3, Steve A. R. Webb4, Christopher C. Butler5 and Alistair Nichol3

Abstract

Background: A rigorous research response is required to inform clinical and public health decision-making during an epi/pandemic. However, the ethical conduct of such research, which often involves critically ill patients, may be complicated by the diminished capacity to consent and an imperative to initiate trial therapies within short time frames. Alternative approaches to taking prospective informed consent may therefore be used. We aimed to rapidly review evidence on key stakeholder (patients, their proxy decision-makers, clinicians and regulators) views concerning the acceptability of various approaches for obtaining consent relevant to pandemic-related acute illness research.

Methods: We conducted a rapid evidence review, using the Internet, database and hand-searching for English language empirical publications from 1996 to 2014 on stakeholder opinions of consent models (prospective informed, third-party, deferred, or waived) used in acute illness research. We excluded research on consent to treatment, screening, or other such procedures, non-emergency research and secondary studies. Papers were categorised, and data summarised using narrative synthesis.

Results: We screened 689 citations, reviewed 104 full-text articles and included 52. Just one paper related specifically to pandemic research. In other emergency research contexts potential research participants, clinicians and research staff found third-party, deferred, and waived consent to be acceptable as a means to feasibly conduct such research. Acceptability to potential participants was motivated by altruism, trust in the medical community, and perceived value in medical research and decreased as the perceived risks associated with participation increased. Discrepancies were observed in the acceptability of the concept and application or experience of alternative consent models. Patients accepted clinicians acting as proxy-decision makers, with preference for invasive interventions increased. Research regulators were more cautious when approving studies conducted with alternative consent models; however, their views were generally under-represented.

Conclusions: Third-party, deferred, and waived consent models are broadly acceptable to potential participants, clinicians and/or researchers for emergency research. Further consultation with key stakeholders, particularly with regulators, and studies focused specifically on epi/pandemic research, are required. We highlight gaps and recommendations to inform set-up and protocol development for pandemic research and institutional review board processes.

PROSPERO protocol registration number: CRD42014014000

* Correspondence: GobatNH@cardiff.ac.uk
1Cochrane Institute of Primary Care and Public Health, Cardiff University, Neaudd Merionnydd, Heath Park Campus, Cardiff, Wales CF14 4YS, UK
Full list of author information is available at the end of the article

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Background

Infectious disease pandemics are recurrent but unpredictable events that have a significant impact on the health, economy and security of societies worldwide [1]. Emerging infections that lead to epidemic or pandemic outbreaks arise at the human-animal interface [2]. The amplification and spread of these diseases can result in outbreaks and epidemics that may develop into a public health emergency. A pandemic occurs when there is global spread of the disease [1]. The World Health Organisation (WHO) monitors and reports pandemics in terms of global phases – inter-pandemic, alert, pandemic and transition [3]. These phases are designed to inform national pandemic risk management strategies and actions. Through all phases, expedient, high-quality epidemiological and clinical research is essential to inform clinical and public health decision-making [4]. Such research has the potential to shift the trajectory of a pandemic [5, 6]. The need to develop research preparedness alongside clinical and public health response preparedness has been recognised increasingly. Some progress has been made in strengthening surveillance systems and in the development and testing of new vaccines. However, the experiences of attempting to conduct research during recent epi/pandemics, such as the 2009 H1N1 influenza pandemic and the 2014 outbreak of Ebola in West Africa, indicate that a timely and effective research response is often not possible [7].

Hospitals and critical care units, in particular, are at the forefront of generating important new knowledge about incidence, outcome, infection control, case presentation, resource utilisation and optimal clinical care and are well placed to provide crucial information to inform both clinical and public health decision-making [8]. Consequently, there is a need to develop both clinical and research pandemic preparedness in critical care units [9]. Clinical research conducted during a pandemic should be held to the same high standards of scientific and ethical rigour as that conducted during non-emergent times. Legislative and moral codes of practice [10] set out the ethical requirements for research, which include that it has value in advancing health or knowledge, that is it methodologically sound and scientifically valid, that the benefit to the individual and society outweighs the risks, and that research participants provide informed consent [11]. Most hospital-based research is subject to review and approval by an independent regulatory body. During the H1N1 pandemic, clinical research was hampered by delays in obtaining these ethical and regulatory approvals, as well as by other factors, such as accessing funding and site recruitment. As a result initial pandemic waves had largely passed by the time recruitment for these studies was ready to commence [10, 13]. As a consequence, recommendations have been made for organised and integrated research preparedness for pandemics and epidemics [14]. This includes the need for operational research capacity, during inter-pandemic periods (‘peace-time’) that can be activated rapidly and effectively when the need arises [7, 10, 15]. Inter-pandemic activities to achieve preparedness include the design and pre-approval of study protocols [16] and the establishment of centralised, rapid regulatory approval processes [4, 7].

One of the challenges to conducting clinical research at varying stages of a pandemic is obtaining valid informed consent from participants affected by the pandemic. Consent is central to the principle of respect for patient autonomy and is an integral part of ethical biomedical research [11]. For informed consent to be valid, participants should receive sufficient information about the study, including the risks involved, for them to make an informed choice about participation; they should understand this information; and they should be competent to decide and to make the decision voluntarily, that is, in the absence of coercion. Potential participants should understand that they have a right to refuse as well as to withdraw from a study without fear of any consequences [11]. However, many forms of illness with pandemic potential have clinical consequences that result in diminished capacity to consent for many affected patients. Moreover, for some research questions there is a time imperative for recruitment of individual research participants. These issues create challenges for planning and conducting research during possible future pandemics.

These challenges are not unique to pandemics, but, rather, are generic to studying any form of critical illness that results in the diminished capacity to consent. There are several alternatives to prospective informed consent that allow research to be conducted ethically when participants lack the capacity to provide informed consent. We identified three alternative models in Table 1, namely, third-party consent, deferred consent and waived consent. These alternative consent processes have made it feasible to conduct emergency or critical care research that would not otherwise be possible [17, 18]. Researchers have highlighted the utility of these models when designing protocols for pandemic research [4], and existing pandemic protocols use hybrid models proportionate to the level of pandemic risk and based on an assessment of patient capacity and availability of a surrogate consenter [19, 20].

We review the evidence on acceptability of these different consent models from the perspective of different stakeholders. In the absence of pandemic-specific research, we have looked to emergency research more broadly as it shares many of the features that we might expect in hospital based pandemic research. These features
We included empirical research using qualitative, quantitative, or both methods that aimed to report the views of potential research participants, their proxy decision makers, clinicians, or research regulators regarding the different models of consent for participation in emergency research. We included paediatric research but excluded neonatal research due to the unique ethical issues arising in this kind of research [24]. English language publications of research conducted in OECD countries from 1996 onward were included. We excluded studies on consent for elective treatment, end-of-life decisions, vaccinations, screening, genetic testing, organ donation and/or other clinical procedures. Studies reporting on research participation that did not include consent, for example, reports of recruitment or efforts at retention, were also excluded, as were descriptive studies reporting on the consent process without evaluating participant experience or studies on the features of consent documents. Finally, the following types of articles were also excluded: opinion pieces, commentaries, editorials, unpublished dissertations, conference abstracts, book chapters, conference reports, protocol papers and reviews.

**Information sources**

We searched the following databases in November 2014: MEDLINE, EMBASE, PsycINFO, Health Management Information Consortium (HMIC) via OvidSP; Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI) via Web of Science SSCI; Cochrane Central; and OpenGrey. We also searched WHO publications via their website, and hand-searched the following journals from October 2012–2014: Intensive Care Medicine, Journal of Medical Ethics, BMC Medical Ethics and Critical Care Medicine. Finally, reference lists of included articles and review articles were mined to identify other relevant citations.

### Table 1 Definitions of terms

| Emergency research | Research including intensive and critical care research that relates directly to a life-threatening or debilitating condition in which there is a time-imperative for intervention. |
|---------------------|-------------------------------------------------------------------------------------------------|
| Capacity to consent | The person should have the capacity to make a choice about the proposed course of action, knows about the study risks, benefits and alternatives, understands that consent is ‘voluntary and continuing permission’, and understands that consent can be withdrawn at any time. |
| Prospective informed consent | The decision (written, dated and signed) to take part in a study, which is taken after the person is fully informed about the study nature, its significance, implications and risks. Informed consent can be given by any person capable of giving consent or, where the person is not capable, by a surrogate decision maker. Oral consent in the presence of a witness may be given in exceptional cases. |
| Third-party consent | Informed consent to research participation is provided by a surrogate or proxy decision maker, for example, a family member or legal representative where the potential participant is unable to provide consent themselves. Proxy consent can also describe the process by which people with the legal right to consent for themselves or as a surrogate can delegate that right to another person. |
| Deferred consent | When a patient is enrolled into a study, and consent is taken later, either from a surrogate decision maker or from the patient when he/she is able to provide informed consent. |
| Waiver of consent | A consent procedure that alters elements of informed consent or waives the requirements to obtain informed consent. For example consent may be waived if the research presents no more than minimal risk of harm to subjects and could not be carried out without a waiver. |
| Exception from informed consent | Permission to research participation is provided by a surrogate or proxy decision maker, for example, a family member or legal representative where the potential participant is unable to provide consent themselves. Proxy consent can also describe the process by which people with the legal right to consent for themselves or as a surrogate can delegate that right to another person. |

Notes on the definitions and their relevance to potential research participants, their proxy decision makers, clinicians, or research regulators regarding the different models of consent for participation in emergency research.

### Methods

Rapid review methodology offers a structured and efficient approach to synthesising evidence to inform decision-making [21, 22]. They are conducted in a shorter time frame than full systematic reviews, but retain most of the methodological rigour by using systematic and reproducible methods. Rapid reviews produce similar conclusions to systematic reviews that are sufficient for policy and clinical decision-making [23]. The principles of a rapid review are that decisions taken to expedite the review should be transparent, that the purpose is clearly enunciated, and that potential limitations are acknowledged. To expedite our review we limited our search by year (1996 onward) and language (English language only), 70 % of citations were screened by a second researcher, a single researcher conducted data extraction and quality assessment of each paper, and our analysis involved description and categorisation as opposed to more formal approaches such as meta-summary [22].

### Eligibility criteria

We included empirical research using qualitative, quantitative, or both methods that aimed to report the views of potential research participants, their proxy decision makers, clinicians, or research regulators regarding the different models of consent for participation in emergency research. We included paediatric research but excluded neonatal research due to the unique ethical issues arising in this kind of research [24]. English language publications of research conducted in OECD countries from 1996 onward were included. We excluded studies on consent for elective treatment, end-of-life decisions, vaccinations, screening, genetic testing, organ donation and/or other clinical procedures. Studies reporting on research participation that did not include consent, for example, reports of recruitment or efforts at retention, were also excluded, as were descriptive studies reporting on the consent process without evaluating participant experience or studies on the features of consent documents. Finally, the following types of articles were also excluded: opinion pieces, commentaries, editorials, unpublished dissertations, conference abstracts, book chapters, conference reports, protocol papers and reviews.
Search strategy
The search strategy was developed using two concepts and synonyms – informed consent and emergency care. In addition, we used an adapted search filter for participant views [25] to enhance the specificity of the search. The full search strategy is available in Additional file 1: Appendix A.

Study selection
A single researcher (NG) reviewed titles and abstracts against the inclusion criteria. Where a decision could not be made on the title and abstract alone, full texts were retrieved. A second researcher (MG) independently reviewed 70% of this sample (n = 482). Discrepancies were resolved by consensus.

Quality assessment
A single researcher completed quality checklists, including risk of bias, for each paper (NG – 48 papers; MG – 3 papers). For surveys, items adapted from Bennett et al. [26] were used, and for qualitative research, the Critical Appraisal Skills Program (CASP) checklist [27] was used.

Data extraction
A single researcher extracted data (study characteristics, consent model, stakeholder group, and acceptability evidence) using a pre-developed data extraction tool (NG – 48 papers, MG – 3 papers).

Analysis
Studies were categorised according to the consent model (informed, third-party, deferred, or waived) and stakeholder group (participants and their proxy decision-makers, clinical and/or research staff and regulators). We grouped studies looking at participant views together with those looking at both participant and their proxy decision maker. Key themes related to the acceptability of each model were summarised across each subgroup [22].

Results
Study selection
We screened 695 titles and abstracts and identified 104 potentially relevant articles. Of these, 52 were excluded due to study features (n = 18), non-OECD country (n = 6), non-emergency research (n = 4), no consent for research participation (n = 3) or no assessment of views (n = 21) (Fig. 1). Our final sample included 52 papers (Tables 2, 3, 4 and 5).

Study characteristics
Our sample comprised studies using quantitative (n = 37), qualitative (n = 11), or mixed methods (n = 4). The

Fig. 1 PRISMA flow diagram of the selection and inclusion of publications
| Reference     | Country                  | Clinical context       | Study design   | Study aim                                                                 | Scenario: real or hypothetical | Study sample                                                                 | Direct experience of trial context or condition | Direct experience of consent model |
|---------------|--------------------------|------------------------|----------------|---------------------------------------------------------------------------|-------------------------------|-------------------------------------------------------------------------------|---------------------------------------------|-----------------------------------|
| 1. Agard 2001 | Sweden                   | Acute myocardial infarction | Mixed methods  | Investigate patient experience of consent process                          | Studies of early phase of treatment for myocardial infarction | 31 trial participants                                                         | Yes                                                                         | Yes                               |
| 2. Blixen 2005 | USA                     | Stroke                  | Qualitative (interview) | Evaluate preferences or values                                              | Hypothetical study – emergency stroke research                  | 12 stroke patients                                                           | Yes                                                                         | No                                |
| 3. Gammelgaard 2004 | Denmark          | Acute myocardial infarction | Qualitative (interview) | Investigate patient experience of consent process                          | Clinical trial comparing intervention (primary angioplasty) with medical strategy (thrombolysis) | 32 trial candidates (23 participants, 9 who did not consent)                  | Yes                                                                         | Yes                               |
| 4. Mangset 2008 | Norway                  | Stroke                  | Qualitative (interview) | Investigate patient experience of consent process                          | Clinical trial evaluating thrombolytic drug treatment for stroke  | 11 trial participants                                                         | Yes                                                                         | Yes                               |
| Survey studies |                          |                        |                |                                                                           |                                |                                                                               |                              |                                   |
| 5. Chenaud 2009 | Switzerland            | ICU                     | Survey (Self-administered) | To evaluate preferences                                                    | Hypothetical scenarios of ICU research                          | 67 patients; 52 relatives from recent ICU admission                          | Yes                                                                         | No                                |
| 6. Gammelgaard 2014 | Denmark          | Acute myocardial infarction | Survey (Self-administered) | Investigate experience of consent process                                  | Clinical trial comparing intervention (primary angioplasty) with medical strategy (thrombolysis) | 181 trial candidates (103 participants, 78 who did not consent)             | Yes                                                                         | Yes                               |
| 7. Gigon 2013 | Switzerland            | ICU                     | Survey (Self-administered) | Evaluate choice                                                            | Hypothetical scenarios of ICU research                          | 185 patients, 125 relatives following ICU discharge                          | Yes                                                                         | No                                |
| 8. Paradis 2010 | USA                    | ED research              | Survey (interview) | Investigate perspectives on consent process                                | Post-trial evaluation. Two clinical trials that evaluated interventions for subarachnoid haemorrhage | 10 studies involving cardiac conditions                                       | Yes                                                                         | Yes                               |
| 9. Schut 2009 | Netherlands            | Stroke                  | Survey (interview) | Post-trial evaluation.                                                     | Two clinical trials that evaluated interventions for subarachnoid haemorrhage | 49 patients; 47 relatives (trial participants)                               | Yes                                                                         | Yes                               |
| 10. Williams 2003 | Australia, New Zealand | Acute myocardial infarction | Survey (interview) | Evaluation of consent for trial                                           | Clinical trial of two antithrombin therapies for acute myocardial infarction | 399 trial candidates                                                        | Yes                                                                         | No                                |
| 11. Yusuf 2000 | Israel                  | Acute myocardial infarction | Survey (Self-administered) | Post-trial evaluation.                                                     | Large trial evaluating therapies for acute myocardial infarction  | 129 trial participants                                                       | Yes                                                                         | Yes                               |
| Clinical research staff and regulators |                |                        |                |                                                                           |                                |                                                                               |                              |                                   |
| Qualitative or mixed methods studies |                |                        |                |                                                                           |                                |                                                                               |                              |                                   |
| 12. Chamberlain 2015 | USA              | Paediatrics – status epilepticus | Qualitative (focus group) | Evaluation during trial                                                     | Pharmacokinetic study evaluating lorazepam for status epilepticus | 18 research staff                                                            | Yes                                                                         | Yes                               |
| Reference | Country | Clinical context | Study design | Study aim | Scenario: real or hypothetical | Study sample | Direct experience of clinical context or condition |
|-----------|---------|------------------|-------------|-----------|--------------------------------|-------------|-----------------------------------------------|
|           |         |                  |             |           |                                |             | Direct experience of consent model            |
| 13. Ali 2006 | UK      | Stroke           | Mixed methods | Inform clinical trial design. | Proposed trial evaluates the effect of routine oxygen supplementation after acute stroke | 49 stroke patients, 24 cases | Yes No |
| 14. Blixen 2005<sup>a</sup> | USA     | Stroke           | Qualitative (interview) | Evaluate preferences or values | Hypothetical study – emergency stroke research | 12 stroke patients | Yes No |
| 15. Koops 2002 | UK      | Stroke           | Mixed methods | Inform study design. | Proposed study evaluates thrombolysis for acute ischaemic stroke | 54 stroke patients and cases | Yes No |
| Survey studies |         |                  |             |           |                                |             |                                               |
| 16. Barnett 2012 | Canada | ICU              | Survey (interview) | Evaluate attitude or opinion | Hypothetical scenarios of ICU research | 136 surrogate decision makers of critically ill patients (adults and children) | Yes No |
| 17. Birs 2009<sup>b</sup> | USA     | Status seizure   | Survey (self-administered) | Part of a public consultation prior to trial initiation | Proposed trial evaluates pre-hospital intervention for status seizures | 1901 community members | No Some |
| 18. Chenuaud 2007<sup>c</sup> | Switzerland | ICU             | Survey (Self-administered) | Evaluate preferences | Hypothetical scenarios of ICU research | 67 patients, 52 relatives from recent ICU admission | Yes No |
| 19. Clark 2013 | UK      | Neurosurgery     | Survey (Self-administered) | Part of a public consultation prior to trial initiation | Proposed study evaluates surgical techniques | 171 patients and cases in neuro-surgical clinic | No No |
| 20. Gigos 2013 | Switzerland | ICU              | Survey (Self-administered) | Evaluate choice | Hypothetical scenarios of ICU research | 185 patients, 125 relatives following ICU discharge | Yes No |
| 21. Kamarainen 2012<sup>d</sup> | Finland | Cardiac arrest   | Survey (Self-administered) | Post-trial evaluation. | Trial evaluated pre-hospital intervention for cardiac arrest | 11 patients; 17 consent providers; 13 physicians (trial participants) | Yes Yes |
| 22. Permer 2010 | Denmark | ICU              | Survey (Self-administered) | Assess attitudes | Hypothetical trials and new medications | 42 need of 41 of unconscious ICU patients | Yes No |
| 23. Scales 2009<sup>e</sup> | Canada | Critical illness | Survey (interview) | Survey preferences | Hypothetical study scenarios of research during critical illness | 240 survivors of critical illness | Yes No |
| 24. Schats 2003<sup>f</sup> | Netherlands | Stroke          | Survey (interview) | Post-trial evaluation, Attitudes survey | Two trials that evaluated interventions for subarachnoid haemorrhage | 49 patients; 47 relatives (trial participants) | Yes Yes |
| 25. Stephenson 2007 | Australia | Emergency care   | Survey (self-administered) | Hypothetical scenarios of critical care research | | 185 patients | Possible No |
Table 3: Characteristics of included studies - third-party consent (Continued)

| Study | Country | Research Type | Method of Consent | Method of Data Collection | Evaluation Focus | Study Population | Ethical Approval |
|-------|---------|----------------|------------------|---------------------------|-----------------|-----------------|-----------------|
| 26. Burns 2013 | Canada | Pandemic research | Survey (self-administered) | Evaluate experiences, beliefs and practices | Hypothetical – pandemic research | 168 administrative and clinical staff involved in H1N1 pandemic research | Yes Yes |
| 27. Cook 2008 | Canada, Australia, New Zealand | Critical illness research | Survey (self-administered) | Evaluate experiences, beliefs and practices | Hypothetical – enrolment of critically ill children and adults | 264 clinicians caring for critically ill patients | Yes Yes |
| 28. Duffett 2011 | Canada | Critical care research | Survey (self-administered) | Evaluate attitudes and beliefs | Hypothetical scenario of double-blind, placebo-controlled, RCT evaluating single dose of medication perceived by REB as minimal risk | 98 ICU researchers, 52 members of hospital research ethics boards. | Yes Possible |
| 29. Kompanje 2005 | Netherlands | Traumatic brain injury | Survey (self-administered) | Evaluate opinions | Hypothetical – clinical emergency care | 79 neuro-trauma clinical staff across 19 European countries | Yes Possible |

*compares different consent models
*compares different stakeholder groups
*paediatrics

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Table 4 Characteristics of included studies – deferred consent

| Reference | Country | Clinical context | Study design | Study aim | Scenario: real or hypothetical | Study sample | Direct experience of clinical context or condition | Direct experience of consent model |
|-----------|---------|------------------|--------------|-----------|-------------------------------|-------------|-------------------------------------------------|----------------------------------|
| 30. Woolfall 2014 | UK | Paediatric – status epilepticus | Qualitative (focus groups, interviews) | Inform study design | Proposed trial evaluating new treatment for status epilepticus | 17 parents | Mixed | No |
| 31. Chenaud 2009 | Switzerland | ICU | Survey (Self-administered) | Evaluate preferences | Hypothetical scenarios of ICU research | 67 patients, 52 relatives | Yes | No |
| 32. Gamble 2012 | UK | Meningitis | Survey (Self-administered) | Investigate views | Proposed trial evaluating two currently used treatments for emergency resuscitation and treatment | 68 families | Yes | No |
| 33. Gigon 2013 | Switzerland | ICU | Survey (Self-administered) | Evaluate choice | Hypothetical scenarios of ICU research | 185 patients, 126 relatives | Yes | No |
| 34. Potter 2013 | Australia | ICU | Survey (Self-administered) | Post-trial evaluation | Clinical trial evaluating two strategies for maintaining blood sugar in ICU | 210 trial participants | Yes | Yes |
| 35. Scales 2009 | Canada | Critical Illness | Survey (Interview) | Survey preferences | Hypothetical study scenarios of research during critical illness | 240 survivors of critical illness | Yes | No |
| 36. Cook 2008 | Canada, Australia, New Zealand | Critical Illness | Survey (Self-administered) | Evaluate experience, beliefs, and practices | Hypothetical – enrolment of critically ill children and adults | 284 clinicians caring for critically ill patients | Yes | Yes |
| 37. Duffett 2011 | Canada | Critical care research | Survey (Self-administered) | Evaluate attitudes and beliefs | Hypothetical scenario of double-blind, placebo-controlled RCT evaluating single dose of medication perceived by REB as minimal risk | 98 ICU researchers, 52 members of hospital research ethics boards | Yes | Possible |
| 38. Woolfall 2013 | UK | Paediatric – status epilepticus | Survey (Self-administered) | Evaluate views and experiences | Hypothetical | 45 clinical staff | Yes | Mixed |

*compares different consent models
*paediatrics
| Reference | Country | Clinical context | Study design | Study aim | Scenario real or hypothetical | Study sample |
|-----------|---------|------------------|--------------|-----------|------------------------------|--------------|
| Blixen 2005 | USA | Stroke | Qualitative (interview) | Evaluate preferences or values | Hypothetical study – emergency stroke research | 12 stroke patients | Yes | No |
| Dickert 2009 | USA | Cardiac arrest | Qualitative (interview) | Assess views | Hypothetical study scenarios for research emergency research | 22 sudden cardiac death survivors | Yes | No |
| Kasner 2011 | USA | Acute neurologic emergency | Qualitative (focus group) | Evaluate views on community consultation | Hypothetical study | Patients with previous stroke or brain injury, their families, and people at risk for traumatic brain injury (n = 40) | Yes | No |
| Morris 2004 | USA | Paediatrics | Qualitative (focus group and interview) | Public consultation | Proposed in-patient paediatric resuscitation clinical trial | 23 parents from PICU of children who had been resuscitated; 33 staff | Yes | No |
| Raymond 2010 | USA | Paediatric resuscitation | Mixed methods | Evaluation of public disclosure | Proposed in-patient resuscitation clinical trial | 93 parents attending a PICU | Yes | No |
| Richardson 2005 | USA | Cardiac arrest | Qualitative (focus group) | Explore attitudes about emergency research without consent | Clinical trial evaluating pre-hospital intervention for cardiac arrest | 42 participants from community where study being conducted | No | No |
| Shah 2003 | USA | Emergency | Qualitative (content analysis) | Recommendations for public disclosure | Documentation for real studies | 4 studies from repository of mandatory documents | N/A | N/A |
| Survey studies | | | | | | |
| Abboud 2006 | USA | Cardiopulmonary arrest | Survey (interview) | Evaluate willingness to participate | Hypothetical scenarios – intervention resuscitation research | 207 Patients attending an emergency department and a 213-ganic clinic | Mixed | No |
| Baxen 1999 | USA | Paediatric | Survey (interview) | Public consultation (feasibility testing) | Hypothetical clinical trial evaluating treatment for posttraumatic sequelae | 237 Patients of children treated in the emergency department | Yes | No |
| Biss 2009 | USA | Status seizure | Survey (self-administered) | Part of a public consultation prior to trial initiation | Proposed trial evaluates pre-hospital intervention for status sequelae | 1951 community members | No | Some |
| Booth 2005 | UK | Cardiac arrest | Survey (self-administered) | Assess attitudes | Hypothetical – emergency research | 361 patients attending an emergency department | No | No |
| Bulger 2009 | USA | Resuscitation | Survey (interview) | Public consultation | Clinical trials evaluating pre-hospital interventions for cardiac arrest and traumatic injury | 2418 representative sample of community | No | No |
| Study ID | Country | Study Type | Data Collection Method | Study Objectives | Setting | Consent Waived? | Number of Participants | Relevant Details |
|----------|---------|------------|------------------------|------------------|---------|----------------|-----------------------|-----------------|
| 51. Dickert 2013 USA | Status epileptics | Survey (interview) | Assess experience and effect of public consultation | Clinical trial of a pre-hospital comparing pharmacological interventions for status epileptics | 24 patients, 37 surrogate decision makers | Yes | 2612 community consultation participants | No |
| 52. Dickert 2014b USA | Acute traumatic brain injury | Survey (various methods) | Survey nested in public consultation | Clinical trial evaluating progesterone for treatment of traumatic brain injury | No | No | 130 community meeting attendees | No |
| 53. Longfield 2008 USA | Traumatic haemorrhagic shock | Survey (self-administered) | Description of public consultation | Clinical trial evaluating a pre-hospital intervention for traumatic haemorrhagic shock | Yes | Yes | Convenience sample of 530 patients attending a hospital emergency department | No |
| 54. McClure 2008 USA | Reanimation | Survey (interview) | Evaluation of views and public awareness of EIC research | Studies conducted under waived consent (details unclear) | No | No | Convenience sample of 530 patients attending a hospital emergency department | No |
| 55. Morris 2006 USA | Paediatric resuscitation | Survey (interview) | Assessment of feasibility of public consultation | Hypothetical scenarios of in-patient resuscitation clinical trials | Yes | No | 91 parents attending a PICU | No |
| 56. Nallison 2013 USA | Cardiac arrest | Survey (interview or self-administered) | Evaluation of patient opt-out experience | Clinical trial evaluating a pre-hospital intervention for cardiac arrest | 46 community members who had opted out of participation in a study conducted under waived consent. | No | No | Convenience sample of 530 patients attending a hospital emergency department | Mixed |
| 57. Ramsey 2011 USA | Emergency research | Survey (interview) | Evaluation of public consultation methods | Clinical trials conducted under waived consent (details unclear) | Community where study being conducted (Baseline, n = 350, 11 months later, n = 320) | No | No | Convenience sample of 530 patients attending a hospital emergency department | No |
| 58. Scales 2009 Canada | Critical illness | Survey (interview) | Survey preferences | Hypothetical study scenarios of research during critical illness | Yes | No | 240 survivors of critical illness | No |
| 59. Smithline 1998 USA | Emergency research | Survey (interview) | Evaluate opinions | Hypothetical study scenario of acute care research | No | No | Convenience sample of patients in an emergency department 212 | No |
| 60. Triner 2007 USA | Traumatic haemorrhagic shock | Survey (self-administered) | Evaluation of effectiveness of public disclosure | Clinical trial evaluating a pre-hospital intervention for traumatic haemorrhagic shock | Mixed | No | Convenience sample of patients attending emergency department 497 | No |

Clinical, research staff or regulators

Qualitative studies

| Study ID | Country | Study Type | Data Collection Method | Study Objectives | Setting | Consent Waived? | Number of Participants | Relevant Details |
|----------|---------|------------|------------------------|------------------|---------|----------------|-----------------------|-----------------|
| 61. McClure 2007 USA | Reanimation | Qualitative (interviews) | Evaluate experience | Hypothetical - based on experience of protocol review | 10 institutional review board members | Yes | Yes | No |
| 62. Cook 2006 Canada, Australia, New Zealand | Critical illness | Survey (self-administered) | Evaluate experience, beliefs, and practices | Hypothetical - enrolment of critically ill children and adults | 284 clinicians caring for critically ill patients | Yes | Yes | No |
| 63. Deleo 2007 USA | Reanimation | Survey (self-administered) | Understand attitudes | Hypothetical - based on experience of protocol review | 69 research ethics board chairpersons | Yes | Mixed | No |
Table 5 Characteristics of included studies - waived consent (Continued)

| Study          | Country | Condition                          | Study Method                       | Research Plan                                                                 | Number of Participants | Waiver | Possibility |
|----------------|---------|------------------------------------|------------------------------------|-------------------------------------------------------------------------------|------------------------|--------|-------------|
| 64. Dickert 2014a | USA     | Status epilepticus                 | Survey (self-administered)         | Assess views and experience of public consultation                           | 28 research staff      | Yes    | Yes         |
| 65. Duffett 2011a,b | Canada  | Critical care research             | Survey (self-administered)         | Evaluate attitudes and beliefs                                                | 98 ICU researchers; 52 members of hospital research ethics boards. | Yes    | Possible    |
| 66. Kampaie 2007 | Netherlands | Traumatic brain injury              | Survey (self-administered)         | Evaluate opinions and experience of research staff                           | 70 neuro-trauma clinical staff across 10 European countries. | Yes    | Possible    |
| 67. Schmidt 2009 | USA     | Severe traumatic injury            | Survey (self-administered)         | Real study of pre-hospital intervention for severe trauma                    | 814 emergency medical technicians participating in the trial.       | Yes    | Yes         |

*a compares different consent models  
*b compares different stakeholder groups  
c paediatrics
number of participants in the studies ranged from 10 to 54 for qualitative studies and from 11 to 2,612 for survey studies. Several studies covered more than one consent model (n = 9) or considered more than one stakeholder view (n = 2).

Fewer studies considered the perspectives of clinical or research staff compared with potential research participants, and just one study included regulator perspectives of third-party and deferred consent [28].

Quality assessment
The quality of reporting of qualitative studies was generally high with most studies and provided a clear statement of research objective (n = 13; 93 %), appropriate use of qualitative methodology (n = 13; 93 %), and evidence of rigorous analysis (n = 9; 64 %).

The quality of reporting for survey studies was variable. The majority reported clear study objectives (n = 34; 95 %), methods of survey administration (n = 38; 100 %), and data analysis (n = 33; 86 %). While most papers gave some description of the research tool (n = 31; 82 %), just over half (n = 21; 55 %) described how the tool was developed and pretested (n = 23; 60 %). Few papers (n = 6; 16 %) described efforts to validate these tools. Limitations across most studies included unclear or limited representativeness of the sample (n = 21; 55 %), influence of non-response bias (n = 21; 55 % reported this) and unclear or limited generalizability of findings (n = 32; 84 %).

We did not exclude any studies on the basis of our quality assessment.

Prospective informed consent
Potential research participants
Included studies evaluated the experience of patients who had the capacity to consent to emergency research participation, for example, myocardial infarction, stroke or general ICU research (n = 11) [29–39]. Much of this research was conducted with patients who had been approached to participate in trials, including both those who had consented and, in some cases, those who had not [32, 38, 39]. Views about the acceptability of prospective informed consent were mixed. While some participants expressed the importance of being given the opportunity to consent, saying that it was important for maintaining dignity [31, 38], others were opposed to being asked to make such a decision in the face of severe illness, with some even indicating that it was immoral [29, 38].

Even when a patient did provide consent, however, the process arguably might not have met the requirement for patients to be fully informed before doing so [29, 32, 36–38]. Evaluations of two clinical trials investigating treatments for acute myocardial infarction found that 19 % of 367 [36] to 28 % of 103 [32] research participants and 7 % of 78 [32] to 8 % of 32 [36] of non-participants read the information sheet, and a mismatch existed between the educational level required to comprehend the information sheet and that of the majority of participants in one study [36]. However, the perception of participants in other trials was that they were capable and sufficiently informed to make a decision and had enough time to do so [32, 34, 39].

Research staff and regulators
Researchers and clinicians highlighted similar concerns about how truly informed parents were when providing consent in paediatric emergency research [40]. High levels of parental distress and anxiety, lengthy and detailed documents, and the high-pressured clinical environment were key barriers identified to this consent process. No papers assessed the views of regulators or of researchers in adult populations in emergency research where patients were deemed to have capacity.

Third-party consent
Potential research participants
Two survey studies on consent in the ICU setting reported that more than 85 % of research participants and their relatives found third-party consent to be acceptable (87 % of 240 [41] and 85 % of 137 [41]). There was a small decline in acceptability when risk increased (greater risk of complications in a placebo controlled randomised controlled trial (RCT) or participants had less time to decide (<3 hrs versus 24 hrs) [42]. Patients (n = 240) who had survived critical illness also indicated third-party consent as their preferred consent model in a low- (76 %) and higher- (81 %) risk study and where two low-risk treatments were compared (77 %). The study reporting the most negative views was a questionnaire study involving people in waiting rooms at emergency departments and intensive care units (ICUs) in Australia. In response to a hypothetical question about how they would feel about a relative providing consent for them to be involved in research in the event of a critical illness, 26 % were strongly in favour, 55 % were neutral, and 19 % were against this [43]. No consistent demographic factors associated with acceptability were noted across studies.

Members of the public consulted about study design were accepting of third-party consent and the need for alternative consent models, considering them necessary to feasibly conduct emergency research [44–47]. Patients and carers involved in the design of a low-risk (oxygen supplementation) [46] and a higher-risk (thrombolysis) [47] study saw value in the need for stroke research and for adaptations to informed consent processes that might make such research feasible. A survey conducted as part of community consultation for a trial evaluating
In order to feasibly conduct critical care research, however, clinical researchers endorsed third-party consent models. Research staff and regulators noted the burden on the proxy decision maker [31, 33, 49]. A preference for two decision makers, particularly when patients and/or family members expressed their ability to make these decisions due to the emotional impact of making a decision at such a time. In a small study of patients who had experienced out-of-hospital cardiac arrest, all patient respondents (100 %, n = 11) agreed (at least to some extent) that the consent provider was able to consent on their behalf, and 88 % of spouses (n = 16) agreed that they were capable of providing consent [48]. However, the clinicians were more sceptical about spouses’ ability to make these decisions due to the emotional impact of making a decision at such a time. In other studies patients and/or family members expressed a preference for two decision makers, particularly when a study is invasive or of higher risk, as this may alleviate the burden on the proxy decision maker [31, 33, 49].

Deferred consent

Potential research participants

Participants in a low-risk observational study in Australia reported high levels of satisfaction with their enrolment using deferred consent [53]. The majority of these participants would have consented to participate if asked prior to enrolment (95.6 %, n = 204), reported a positive experience with their method of enrolment, and were satisfied with who provided consent on their behalf (92.7 %, n = 202), and were satisfied with the decision taken on their behalf (93 %, n = 201). Patients indicated varying degrees of acceptability to enrolment using deferred consent for hypothetical studies. A greater proportion of patients preferred a deferred
The acceptability of deferred consent was also dependent on the perceived risk of the intervention. In both studies, participants considered deferred consent acceptable for drug trials (69 %, n = 42), but a third of these respondents would not endorse this consent model for a new drug (28 %, n = 29) [49].

Two studies considered the acceptability of deferred consent in the design of trials in pediatric emergency research. Results of a survey with families whose child had experienced bacterial meningitis or meningococcal sepsicaemia indicated that the majority (67 % of 68) would be willing for their child to be enrolled under deferred consent in a trial that evaluated the effectiveness of two treatments already routinely in use for that condition (Gamble) [54]. In the event of their child’s death, 66 % of the bereaved respondents (n = 19) compared with 37 % of non-bereaved respondents (n = 49) would have wanted to be told of their child’s enrolment at some time. In a qualitative study examining parental views on a proposed trial that aimed to evaluate an anticonvulsant not yet in standard use for pediatric seizures, participants considered deferred consent acceptable [55]. They recognised the need for this model for the feasible conduct of research, saw value in research to inform treatment for other children, and expressed trust in clinicians.

The acceptability of deferred consent was also dependent on the perceived risk of the intervention. In both studies, recommendations included the need for sensitivity around timing of obtaining consent and, among bereaved parents, of the individuality of the grief process [54, 55].

Potential research participants
The acceptability of waived consent research was strongly influenced by participant beliefs and experiences, for example, with involvement in research and/or receiving medical care [70]. Several studies showed a discrepancy between the concept of waived consent and its application. For example, focus group participants expressed strong ethical objections to research conducted with waived consent, but these views shifted when discussing their personal experiences [70]. Likewise, discrepancies existed between the proportion of respondents who considered waived consent acceptable and the proportion that would be willing to participate [44, 61, 66, 67]. For example, of the attendees who took part in a public consultation for a trial evaluating pre-hospital interventions for seizures, 35.4 % of 1,901 gave support for the concept of enrolment under waived consent, whereas 51 % indicated willingness to take part [44]. However, 82 % (n = 1,901) of the respondents in this study viewed it as beneficial. In a public survey for resuscitation research, 34 % (n = 530) of respondents endorsed enrolment without prior consent, whereas 70 % would be willing to participate [67]. This dropped to 49 % when the study involved a new treatment,
suggesting that perceptions of risk may influence decision-making. In contrast, a higher proportion of participants in a public consultation for a trial evaluating pre-hospital intervention for severe traumatic injury were reported to ‘not object’ to the concept of enrolment without prior consent (66 % of n = 150). Of these, 82 % (n = 150) were willing for the trial to continue; however, < 67 % would want to be enrolled or be willing to enrol their family member [66]. The authors noted potential confusion, particularly among elderly attendees about the concept of waived consent for research. Taken together, these findings might suggest that while people are more conservative in accepting the concept of waived consent, possibly in a desire to protect the rights of others, they are inherently altruistic in their desire to contribute to research [44, 67].

Qualitative studies with patient populations most likely to be affected by research conducted under waived consent studies have suggested altruism and trust in the medical community as key elements of patient’s decision-making [62, 63, 65, 77]. In a small qualitative study with stroke patients, interviewees were almost unanimous (92 %, n = 11) in their endorsement of physicians consenting to their participation if a surrogate decision maker was not available [77]. Another qualitative study with sudden cardiac death survivors found that patients were more concerned about risks and benefits of study participation than with the method of consent or aspects of study design such as randomisation [62]. Some interviewees in this study were also accepting of a hypothetical study that involved some risk (1 in 10 000 risk of death) but little prospect of direct benefit. Results from a focus group study with stroke or brain injury patients and their families, as well as those at risk of such injury, suggest high levels of acceptability of research conducted under waived consent [65]. This study also highlighted confusion about key research concepts, such as equipoise and randomisation, and identified the potential for therapeutic misconception, where participants perceive they will receive better treatment by their participation in the trial. When interviewed, participants and surrogate decision makers who had been involved in a clinical trial comparing pre-hospital pharmacological interventions for status epileptics reported awareness of the trial prior to enrolment [63].

We identified three studies concerned with paediatric in-patient resuscitation research, all of which involved parents reported from PICU, the community most likely to be affected by this research [58–60]. Parents endorsed the need for the research to be conducted without explicit consent. They described high levels of distress and feeling overwhelmed and fearful among the reasons for not being able to take in information and provide prospective consent [59]. However, they would want to be made aware that the research was taking place and have the option to opt out. A small group of parents who would choose to opt out (15 % of 91) described the stress related to that decision, the desire for the physician to choose their child’s treatment, and not wanting to be a guinea pig as reasons for their choice [58]. A range of methods for raising awareness of active studies have been used including posters in the waiting room, brochures, and verbal explanations of the study on admission. Following this approach, the majority of parents surveyed in a PICU were aware of a paediatric resuscitation study being conducted under waived consent (81 % of 93) [60].

Research staff and regulators
In a European survey, waived consent was seen as acceptable for emergency traumatic brain injury research by the majority of respondents (64 %, n = 79); however, 95 % indicated that proxy consent should also be sought later [50]. Waived consent was considered effective and feasible to increase enrolment of critically ill children and adults into clinical studies; however, views on the ethical acceptability of this approach varied among clinicians and researchers across Australia and New Zealand,
In a hypothetical low-risk RCT, regulators (4.1%, n = 52) and researchers (22.4% n = 98) were least comfortable approving research conducted under waived consent compared with other consent models.

In the United States, regulators experienced protocols including waived consent as more complex and time consuming to review [78, 79], with one study reporting a mean time of 8.8 h, compared with 2.3 for studies not conducted under EFIC [79]. A key challenge in applying the law involved determining what constitutes adequate community consultation and public notification [78]. Different methods, at times in combination with each other, are used to achieve this goal [76, 79]. Regulators perceived the US final rule regulation as ethically acceptable in that it protected subjects (72%, n = 46 [78, 79] and correctly balanced this protection with the need to conduct research (69%, n = 45 [79]). We did not identify any studies of regulator views of waived consent in Europe.

**Discussion**

We reviewed publications on stakeholder acceptability of consent models for emergency research participation that might inform pandemic research preparedness. A recognition exists across all stakeholder groups that emergency research calls for a derivation of prospective informed consent that is appropriate to this context. Our findings suggest that alternative consent models are broadly acceptable to potential research participants and clinical or research staff. Less is known about regulator views; however, one study suggests they may be more conservative in approving third-party and deferred consent [28]. Our findings also highlight issues and recommendations that might enhance the acceptability of these consent models and encourage recruitment in emergency research that is likely to be applicable to future epidemic/pandemic research.

Critically ill patients are a particularly vulnerable population, and the ethical integrity of informed consent processes is challenging even for those who have capacity to provide consent prospectively [39]. However, many studies included in our review suggest that potential research participants do understand the difficulties in conducting emergency research, support the need for it, and accept the need for alternative consent models to feasibly conduct it. Willingness to participate in research and acceptance of alternative consent models was motivated by perceived value in the importance of conducting research. Furthermore, participants appear motivated by altruism, by trust in the medical community, and, importantly, by perception of the risks and benefits to taking part [62, 80]. In many included studies, the acceptability of consent models decreased in higher risk scenarios. Issues of risk and trust are open to multiple interpretations of meaning and several qualitative studies revealed complex issues such as therapeutic misconception, where patients tend to believe they will receive superior treatment if they volunteer for a clinical trial. In a pandemic, this might be particularly salient with overestimations of the potential benefits of novel, but unproven treatments, with patients viewing research participation as a means to gain access to these treatments.

Direct experience also influenced the perception of acceptability to participants, researchers, or regulators. For example, a higher proportion of participants enrolled in a study using deferred consent found the model acceptable [53] in comparison with other studies that evaluated hypothetical scenarios [33, 41]. In addition, greater acceptability of deferred consent was observed among those paediatric clinicians who had experience of the model than those who did not [56]. Among research regulators, acceptability of waived consent has developed over time through experience of interpreting relevant legislation [78, 79]. It is important, therefore, not only to continue to evaluate the experience of these different stakeholder groups but also to ensure representation of such individuals in the development and regulatory evaluation of study protocols. Additionally, on-going research during inter-pandemic periods is needed to evaluate the way in which these models were implemented and the experience of all stakeholders in using them.

**Application to a pandemic context**

Most of the included studies were conducted in emergency care but non-pandemic contexts, and the extent to which we can generalise these findings to pandemic emergency research requires investigation. Ethical acceptability is determined in part by the context in which an action occurs, and different norms might be acceptable for research conducted when a pandemic threat or impact is low compared with when it is moderate or high [19]. However, as others have argued, it is the capacity of the patient rather than the urgency of a pandemic context that determines the acceptability of using alternative consent models in research [16]. Not all acutely ill patients presenting to emergency departments will lack capacity, and findings from our review were mixed about whether potential participants preferred to consent themselves or for another to decide on their behalf. Further, these consent models are not necessarily applicable in other pandemic research contexts, such as in non-emergency situations or in primary care, where patients might be less unwell and more likely to have capacity for providing prospective informed consent. Rather, the acceptability of the consent process in all settings is judged proportionate to the likely outcome of the illness and the likely burden associated with the intervention under evaluation. For example, waived
consent may be the preferred consent method for clinical trials of routinely used treatments with an established safety record, but unproven for the pandemic pathogen [20]. Findings from our review were not adequate to assess the acceptability of waived consent in such a context. Moreover, pragmatic adaptations are likely to be made. For example, in a pandemic influenza outbreak, while third-party consent might be preferable, this consent might be obtained through different communication media such as verbally, by telephone or through translators [4, 19]. Findings from our review could not capture the utility or acceptability of these pragmatic solutions.

Policy and legislative frameworks that guide the inclusion of alternatives to prospective informed consent in study protocols vary across countries and regions, impeding the ability to conduct harmonised multi-site trials. This has been a particular concern in Europe with regard to the legislative context guiding clinical trials in European Union (EU) member states and its impact on emergency research. The EU Clinical Trials Directive 2001/20/EC outlined the need for proxy consent before enrolling participants who lack capacity, with no accommodation for studies in which treatment initiation needed to occur within a narrow window of time [81]. The directive was not legally binding in all member states. Consequently, about half of the EU member states addressed this by permitting deferred consent in their national law, whereas others made no provisions for emergency research [82]. This lack of harmonization presents a barrier to setting up and conducting multi-site, clinical trials for pandemic research across Europe, as researchers must navigate the different legal requirements for obtaining consent that are ratified in national law. The European Parliament has now approved new legislation in the form of a regulation (No. 536/2014), which will be legally binding in all EU member states and will allow deferred consent for emergency research under certain circumstances [83]. This is an important step for those wishing to set up pandemic research infrastructures across Europe, where the need for a coordinated approach is considered essential.

In addition to the need for scientific and ethical rigour, pandemic research needs to be efficient in its design feasibility and speed of set up [4, 84]. Clinical trials, for example, need to be recruiting within weeks of pandemic onset to inform care decisions within that same pandemic. The strain on hospital and ICU capacity to respond to surge demands for clinical services will escalate as the pandemic impact progresses [9, 10]. Ethically, research processes should not rely unduly on clinician time that would be best spent treating patients. Research designs aligned with clinical practice, such as comparative effectiveness research, [85] may allow efficient evaluation of routinely used treatment procedures. Adaptive platform trials, set up during inter-pandemic ‘peacetime’ might also expedite inclusion and investigation of novel treatments once an epidemic or pandemic is underway [86, 87]. A platform trial is essentially a trial infrastructure in which various interventions are evaluated within a master protocol. Interventions may be added or dropped once emerging outcome data provides a pre-specified sufficiently precise estimate of effectiveness or the lack thereof. Response-adaptive trials alter the proportion of patients randomised to various arms depending on emerging trial data, with more participants randomised to the more successful intervention. These innovative study designs have raised unique ethical issues that have been debated [88, 89], including questions about the validity of informed consent procedures. Adaptive trials, for example, have been described as more complex to explain to patients, threatening patient’s ability to absorb and understand what is being asked of them [88, 90]. However response-adaptive designs may go some way to address therapeutic misconceptions by narrowing the gap between what participants believe (that trial participation will improve their outcomes) and what they experience (that they will have a greater chance of being allocated to a successful intervention) [91]. Further investigation into the preferences, experiences and acceptability of consent processes for novel study designs is required.

While new study designs and alternative consent models might hold the most promise for enabling pandemic research to progress, they also attract more intensive regulatory review than more traditional designs [78, 92]. Findings from our review suggest that, while the experiences of regulators has not been well evaluated, the regulators appear to be more cautious in their judgments. This is perhaps not unexpected: regulatory bodies are tasked with protecting the rights, safety and dignity of research participants, and their decisions impact public confidence and trust in science. However the views of the public, particularly among research participants with direct experience of the use of these alternative consent models, should inform regulatory decisions around acceptability. Questions arise, however, about how best to engage with members of the public so that they might contribute to these decisions in a meaningful way.

While there is still much to learn in this complex arena, it may be possible to suggest a few areas of good practice informed by previous research in this area. Recommendations might include the following: prospective informed consent in emergency research where patients have capacity should respect patient preference for verbal summary over written study information [29, 32] and the opportunity to discuss the study prior to giving consent [37]. When enrolling participants using third-party consent, study information should be provided to...
participants or their legal guardians after the acute phase of illness [48], decision concordance cannot be presumed [31, 33, 93–95], and involving a second decision maker, such as a treating clinician, might alleviate the burden [96] for proxy decision makers [31, 33]. Sensitivity to timing and the quality of the communication process, particularly for bereaved relatives, is required when implementing deferred consent [55]. Community consultation and engagement should use multiple methods, the majority of which should involve two-way communication [69, 75, 76]. Partnering with community members who represent target populations might enhance a study’s exposure and acceptability [69]. Strategies for ensuring awareness for on-going studies need to be developed [72] to better understand the demographics and views of people who opt-out, thereby allowing for targeted public awareness efforts [68].

Our review has also identified areas for future study. Stakeholder perceptions related specifically to consent models for pandemic-related research need evaluating. Further research on regulator experience and views is also required, particularly in the context of legislative changes across Europe. Article 35 of Regulation No. 536/2014, effective from May 2016, makes provision for obtaining informed consent in emergency situations that will be legally binding across all member states [83]. Under this regulation, deferred consent will be legally acceptable for emergency trials conducted in EU member states; however, there is a lack of research with adults who have experienced deferred consent. Furthermore, research on the unique set of challenges for implementing alternative consent models in paediatric emergency research, including the views of children or young people, is also indicated.

Strengths and limitations
Other systematic reviews have been conducted in this area that present a thorough and detailed examination of some samples included in our review [80, 97, 98]. However, our review set out to map the breadth and direction of evidence on acceptability from multiple stakeholder perspectives and to offer guidance for further research in some key areas not identified in these other works. We developed a comprehensive search strategy that included grey literature; however, this was not exhaustive. Decisions taken to expedite our review may have introduced human error, selection bias, and language of publication bias into our sample. We were unable to assess the effect of publication bias. As appropriate to rapid review methodology, we used narrative synthesis in our analysis [22], which lacks the depth and detail of more formal methods such as meta-analysis or meta-synthesis. The heterogeneity across our sample, in context and in method, makes valid comparisons across studies complex. While most of our sample consisted of qualitative studies and surveys, there is variability in terms of the way these studies were designed, conducted, and reported [26]. For example, the way in which survey questions were framed, the variability in their aims (for example, assessing attitudes, opinions, preferences, or behaviours), the use of hypothetical scenarios, and the different modes of survey administration would all influence the results. While we assessed each survey for quality to judge the validity of findings in their own merit, we did not exclude any studies based on lower quality assessments.

Conclusions
Alternative consent models will be needed to feasibly conduct some types of pandemic research, especially in relation to emergency situations. Potential research participants, their families, clinicians and research staff are broadly accepting of these alternative methods of obtaining consent for emergency research. The views of research regulators are less clear, but it is important for regulators to consider the views of various stakeholders in deciding on the direction of future regulation. Implementing these models requires balancing ethical principles of individual autonomy and social justice. In a pandemic, there may be a stronger imperative to more easily facilitate research that might confer significant benefit to society at large. These inherent tensions will require further research and greater public involvement in order to understand and document a full range of key stakeholder experiences in implementing these models, as well as to consider the acceptability to stakeholders in a pandemic context and to inform regulatory decision-making.

Additional file

Additional file 1: Appendix A. Rapid review full search strategy.
Description of data: record of the search strategy used for each database.

Abbreviations
EU: European Union; ICU: intensive care unit; PICU: paediatric intensive care unit; WHO: World Health Organisation.

Competing interests
On behalf of all authors, the corresponding author states that there is no conflict of interest.

Authors’ contributions
NG designed the study, conducted the search, extracted and analysed the data, and drafted and revised the manuscript. MG designed the study, extracted and analysed data, and developed the manuscript. NF participated in the study design, data analysis, and writing of the manuscript. KH participated in the study design and provided statistical and trial expertise to the reporting of findings. AW participated in the study design and coordination, helped access papers, and reviewed drafts of the manuscript. RM participated in the study design. JT participated in the study design and provided ethical expertise in the reporting of findings. SW provided pandemic research preparedness and clinical expertise in the reporting of findings. CB leads the research team, participated in study design, and provided pandemic research preparedness and clinical expertise in the reporting of findings. AN leads the research team,
participated in the study design, and provided pandemic research preparedness and clinical expertise to the reporting of findings. All authors reviewed and approved the final manuscript.

Acknowledgements

Maia Mann, Sarah Unit for Research Evidence (SURE), Cardiff University, provided methodological guidance and expertise; Prasanth Sukumar is a member of the EARL research team.

This work received funding from the European Union Seventh Framework Programme (FP7) under the project PREPARE (grant agreement No 602625).

Author details
1Cochrane Institute of Primary Care and Public Health, Cardiff University, Neasudd Memorinydd, Heath Park Campus, Cardiff, Wales CF14 4YS, UK.
2College of Biomedical and Life Sciences, Cardiff University, Cardiff, Wales, UK.
3University College Dublin, Dublin, Ireland. 
4University of Western Australia, Perth, Australia.
5Oxford University, Oxford, UK.

Received: 2 July 2015 Accepted: 8 December 2015

Published online: 29 December 2015

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