Author's response to reviews

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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

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Abstract

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

Methods
We conducted a rapid evidence review, using 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, 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. However there were variations depending of differing contextual factors, and acceptability decreased as study risk increased. There were discrepancies between acceptability of the concept and application of alternative consent models. Patients accepted clinicians acting as
proxy-decision makers, with preference for two decision makers as invasiveness increased. Regulators were reportedly more conservative at 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 that should inform set-up and protocol development for pandemic research, and institutional review board processes.

**PROSPERO protocol registration number: CRD42014014000**
Introduction

Infectious disease pandemics are recurrent and unpredictable events that have a significant impact on societies worldwide [1]. A rigorous research response during a pandemic is required to inform both clinical and public health decision-making [2]. There is increasing recognition of the need for alternative approaches to seeking consent in order to feasibly conduct this research. Informed consent for research participation is a fundamental safeguard against unethical research practice [3]. It involves a process of communication that results in a potential research participant’s authorization or refusal to participate in a study based on an understanding of what their involvement entails and in the absence of coercion [4]. Further, participants should have capacity to make this decision.

Alternative consent models (box 1) can improve recruitment to clinical trials [5, 6] and some clinical trials may only be feasible through the use of these approaches. In Europe, current legislation seeks to protect participants who lack capacity, setting out an obligation for researchers to obtain written proxy consent [7]. However in practice this legislation has inadvertently hampered the feasibility of conducting emergency or critical care research [5, 8, 6]. In emergency situations patients experience a severe or life-threatening event or illness and may be incapacitated due to their illness state, its treatment or both [9]. Necessary treatments are often time-sensitive and a proxy decision maker may not be available or may also have diminished capacity to consent on the patient’s behalf. Patients may then be enrolled into a study and consent sought later, from the patient when they are able, from a proxy decision maker or from both, for the patient’s continued participation in the study [9]. In research that comprises no more than minimal risk to participants, research may be conducted in the absence of consent from either the individual or a proxy decision maker [9]. As many trials examine similar treatments with minimal risk to patients (i.e. two different statins in current use), there is an increasing debate suggesting this model should be facilitated [10, 11].
Much like in emergency care research, during pandemics, potential research participants, particularly those requiring hospitalisation, may have diminished capacity and trial therapies may need to be initiated within a short time-frame. In addition, pandemic research frequently offers access to novel treatments and may confer a benefit not only to the participants but also to the wider population. Ethical conduct of such research may involve a different balance between principles of individual autonomy and social justice.

We conducted a rapid evidence review [12-14] of stakeholder acceptability of different consent models for emergency research participation to inform pandemic research planning.

**Methods**

Rapid reviews allow for the swift production of findings, collated using systematic and reproducible methods. They produce similar conclusions to systematic reviews that are sufficient for policy and clinical decision making [15]. The principles of a rapid review are that decisions taken to expedite the review should be transparent, that the purpose is clearly enunciated, and 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 metasummary [13].

**Eligibility criteria**

We included empirical research using qualitative, or quantitative, or both methods that aimed to report the views of potential research participants, their proxy decision makers, clinicians’ or research regulators, regarding 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. English language publications of research conducted in OECD
countries from 1996 onwards 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, e.g. 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 SSI; Cochrane Central; and OpenGrey. We also searched World Health Organisation (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.

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 [16] to enhance the specificity of the search. The full search strategy is available from the corresponding author on request.

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 [17] were used and for qualitative research, the Critical Appraisal Skills Program (CASP) checklist [18] was used.

Data extraction

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

Analysis

Studies were categorised according to consent model (informed, third-party, deferred, 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 acceptability of each model were summarised across each sub-group [13].

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), not consent for research participation (n=3) or no assessment of views (n=21) (figure 1). Our final sample included 52 papers.

**Study characteristics**

Our sample comprised studies using quantitative (n=38), qualitative (n=13) or mixed methods (n=1). The number of participants in the studies ranged from 10 to 54 for qualitative studies and from 11 to 2612 for survey studies. Several studies covered more than 1 consent model (n=9) or considered more than 1 stakeholder view (n=2) (table 1).

Fewer studies considered the perspectives of clinical or research staff compared with potential research participant views, and just one study included regulator perspectives of third-party and deferred consent [19].

**Quality assessment**

The quality of reporting of qualitative studies was generally high with most studies providing 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 of 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 capacity to consent to emergency research participation, e.g. myocardial infarction, stroke or general ICU research (n=11) [20-30]. While some participants expressed the importance of being given the opportunity to consent, saying that it was important for maintaining dignity [22, 29], 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 [20, 29].

Even when a patient does provide consent however, the process arguably might not have met the requirement for patients to be fully informed before providing consent [20, 29, 28, 27, 23]. Only 19% of 367 [27] to 28% of 103 [23] research participants and 7% of 78 [23] to 8% of 32 [27] of non-participants read the information sheet, and there was a mismatch between the educational level required to comprehend the information sheet and that of the majority of participants in one study [27]. Nevertheless, the perception of many patients was that they were capable and sufficiently informed to make a decision, and had enough time to do so [23, 25, 30].

*Research staff and regulators:* Researchers and clinicians highlighted similar concerns about how truly informed parents were when providing consent in paediatric emergency research [31]. 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: Over 85% of research participants, their relatives, and members of the public reported that they found third-party consent to be acceptable [32-34]. 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 [35].

No consistent demographic factors associated with acceptability were noted across studies. Fewer than half of patients (45% of 11) and clinician proxy decision makers (46% of 13) felt consent was necessary at all under emergency research conditions, while 71% of 17 spouses felt some form of consent was necessary [36]. 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 (<3hrs versus 24hrs) [32].

Most respondents wanted the patient to decide about research participation if they were able (75% of 67 patients, 77% of 52 relatives) [22]. However, in a hypothetical study, a third of patients and their relatives (31% of 185) wanted someone other than the patient to give consent, even if the patient had capacity, particularly if the was study invasive [24]. With regard to who should provide third-party consent, differences were again expressed among stakeholders. When asked, patients seemed to have a proxy in mind including support for a physician to act as a proxy decision maker [21, 24]. Invasiveness of a study (i.e. low-risk RCT versus observational research) did not impact preference for who should consent [24]. 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 [36]. 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 proxy decision maker burden [22, 24, 37].

**Research staff and regulators:** Clinical researchers generally endorsed third-party consent models, however they had concerns about the capacity of proxy decision makers to consent on their relative’s behalf, both in a survey related to traumatic brain injury research (hypothetical) (48%, n=78, [38] and in a real low risk trial of therapeutic hypothermia after cardiac arrest (61%, n=13, [36]). Surveyed researchers endorsed third-party consent for a hypothetical trial provided by two independent physicians (46.4%-54.1%, n= 98 ([19]); rated 6, IQR=5,7 on a 7 point scale; n=284,[39]) when a surrogate decision maker was not available, however views on the ethics (4, IQR=3,6, n=284, and feasibility (5, IQR=3,6, n=284,) of this approach varied [8]. In comparison, regulators were significantly more conservative in approving this model of third-party consent in a hypothetical low risk trial (10.0-18.0%, n=52, <0.001)[19].

We identified just one paper specific to pandemic research [40]. In a Canadian cross-sectional survey, 74% of 39 research coordinators and 51% of 139 administrators agreed that alternatives to third-party consent were required in order to effectively recruit participants to pandemic research studies [40]. Just 14.4% of 39 of research co-ordinators and 5.1% 139 of administrators disagreed with this concept. Alternative models would include adaptations to third-party consent e.g. consent being provided by two clinicians, deferred consent or waived consent.

**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 [41]. 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, 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 also indicated acceptability of enrolment using deferred consent for hypothetical studies
(59%-86%, n=185[24], 48%, n=240 [33]) with acceptability decreasing as study invasiveness (50%-59%,
n=185)[24] or risk of complications (29%-32%, n=240) [33] increased. Surveyed relatives of ICU
patients also 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) [37].

Two paediatric studies of hypothetical trials, showed acceptability of deferred consent to parents,
even in the event of bereavement of a child [42, 43]. The majority of respondents indicated they
would be willing for the trial to commence before receiving information on it (67%, n=68) [43].
Parents described trusting paediatric clinicians and reported altruistic motivations for supporting
research participation [43, 42]. Recommendations, particularly around obtaining consent from
bereaved parents, point to sensitivity around timing of obtaining consent and the individualism of
the grief process among these parents [43, 42].

*Research staff and regulators:* Clinicians perceived deferred consent as one of a number of effective
strategies to promote enrolment of critically ill children and adults into clinical studies [39, 44] and
the majority perceived the model as feasible and ethical [39]. Clinicians who had experienced
deferred consent did not perceive an impact on their relationship with parents/ family of the child
(59%, n=27) compared with clinicians who had no experience of this model (22%, p=0.01),
suggesting that perceptions of the model may shift with experience of using it [44]. Regulators were
however less comfortable approving deferred consent for a hypothetical low risk clinical trial, than in
approving research conducted with third-party consent and were more conservative in considering it acceptable (8%, n=52 participants) compared with researchers (43.3%, n=98 participants)[19].

**Waived consent**

Most of the studies that addressed waived consent (n=30) were conducted in the USA (n=28), including four that addressed paediatric research under waived consent [45-48]. These studies are governed by the Federal and Drug Administrative legislation that requires sufficient community consultation and public disclosure of this kind of research. Consequently, of the 22 studies that assessed research participant views [49, 21, 50-59, 33, 60-62], half of these (n=9) described public consultations.

*Potential research participants: Acceptability of waived consent research was strongly influenced by participant beliefs and experiences, e.g. with involvement in research and/or receiving medical care [59]. Several studies showed 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 [59]. Likewise there were discrepancies between the proportion of respondents who considered waived consent acceptable and the proportion that would be willing to participate. Some studies suggest greater number of participants would be willing to take part [49, 53, 56], while others showed fewer numbers being willing to participate [55, 61]. In one study, the direction of this effect was dependent on the risk of participating: 84% of 361 participants thought it acceptable for a trial to progress, with 92% willing to enrol on greater than minimal risk study, 97% for a less than minimal risk study [50].

It is a legislative requirement to consult members of the public about research conducted with waived consent in the USA, and different methods have been used to do this. Two-way
communication processes such as public meetings were more acceptable to members of the public than one-way processes such as information via the media or posters [53, 63]. In a small UK survey on public opinion of waived consent for emergency research 62% of respondents approved of public meetings to raise awareness of the research, while just 35% said they would actually attend one (n=362) [50]. Public awareness of on-going studies conducted under a consent waiver was also reported to be generally low [56, 61].

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 [38]. 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, (n=276)[39]. 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 USA, regulators experienced protocols including waived consent as more complex and time consuming to review [64, 65], with one study reporting a mean time of 8.8hrs, compared with 2.3 for studies not conducted under EFIC [65]. A key challenge in applying the law involved determining what constitutes adequate community consultation and public notification [64]. Different methods, at times in combination with each other, are used to achieve this goal [66, 65]. Regulators perceived the US final rule regulation as ethically acceptable in that it protected subjects (72%, n=46 [65], [64]) and correctly balanced this protection with the need to conduct research (69%, n=45 [65]). We did not identify any studies of regulator views of waived consent in Europe.

Discussion
We reviewed publications on stakeholder acceptability of consent models to emergency research participation that might inform pandemic research preparedness. There is recognition 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 [19]. Our findings also highlight key 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 epi/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 [30]. However potential research participants do understand the difficulties in conducting emergency research. They also support the need for it and, when involved in trial design, accept the need for alternative consent models [67, 4]. Direct experience of a consent model may make a difference to how acceptable these models are to participants, researchers or regulators. For example, a higher proportion of participants enrolled in a study using deferred consent found the model acceptable [41] in comparison with other studies that evaluated hypothetical scenarios [33, 24]. There was also greater acceptability of deferred consent among paediatric clinicians who had experience of the model than those who did not [44]. Among research regulators acceptability of waived consent has developed over time through experience of interpreting relevant legislation [65, 64]. It is important therefore to not only 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.
Equally important is to continue to clarify what might make these models more acceptable to key stakeholder groups, each of which holds different roles in the production of high quality, ethically acceptable research. Recommendations include the following: Prospective informed consent in emergency research where patients have capacity should respect patient preference for verbal summary over written study information [20, 23] and opportunity to discuss the study prior to giving consent [28]. When enrolling participants using third-party consent, study information should be provided to participants or their legal guardians after the acute phase of illness [36], decision concordance cannot be presumed [68-70, 22, 24] and involving a second decision maker, such as a treating clinician, might alleviate the burden [71] for proxy decision makers [22, 24]. Sensitivity to timing and the quality of the communication process, particularly for bereaved relatives is required when implementing deferred consent [42]. Community consultation for research conducted under a consent waiver should use multiple methods, the majority of which should involve two-way communication [66, 58, 63]. Partnering with community members who represent target populations might enhance a study’s exposure and acceptability [58]. Strategies for ensuring awareness for ongoing studies need to be developed [61] to better understand the demographics and views of people who opt-out, thereby allowing for targeted public awareness efforts [57].

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 [72]. 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 experienced deferred consent. Further research on the unique challenges of implementing alternative consent
models in paediatric emergency research, including the views of children or young people, is also indicated.

Strengths and limitations

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 fully assess the effect of publication bias. As appropriate to rapid review methodology, we used narrative synthesis in our analysis [13] which lacks the depth and rigor of more formal methods. Our findings provide therefore an overview of the breadth and direction of available evidence and offer a steer for further research.

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. However, the views of research regulators are less clear. 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. Further research is required to understand and document key stakeholder experience of implementing these models as well as to consider acceptability to stakeholders in a pandemic context.

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

Author contributions
Designed the study: NG, MG, AW, NF, CB, KH, AN; Conducted the review: NG, MG, AW; Prepared and analysed data: NG, MG, NF. Wrote first draft: NG. Revised manuscript: MG, NF, KH, SW, CB, AN; All authors approved the final manuscript.
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