Basic Science

EOR | VOLUME 5 | FEBRUARY 2020
DOI: 10.1302/2058-5241.5.180051
www.efortopenreviews.org

EFORT open reviews

A review of informed consent and how it has evolved to protect vulnerable participants in emergency care research

Rajpal Nandra[1]
Alan F. Brockie[2]
Faisal Hussain[3]

- A vulnerable participant in research lacks capacity to consent or may be exposed to coercion to participate. Capacity may be temporarily impaired due to loss of consciousness, hypoxia, pain and the consumption of alcohol or elicit substances.
- To advance emergency care, providing life-threatening measures in life-threatening circumstances, vulnerable patients are recruited into research studies. The urgent need for time-critical treatment conflicts with routine informed consent procedures.
- This article reviews ethical considerations and moral obligations to safeguard these participants and preserve their autonomy.
- A particular focus is given to research methodology to waive consent, and the role of ethics committees, research audits, research nurses and community engagement.
- Research on the acutely unwell patient who lacks capacity is possible with well-designed research trials that are led by investigators who are sufficiently trained, engage the community, gain ethical approval to waive consent and continuously audit practice.

Keywords: capacity; emergency care research; good clinical practice guidelines; informed consent; refusal of treatment; vulnerable participants

Cite this article: *EFORT Open Rev* 2020;5:73-79.
DOI: 10.1302/2058-5241.5.180051

Introduction

Healthcare research is undertaken to advance treatment of human disease. In the absence of such research, the efficacy of disease treatments would undoubtedly plateau. Innovation to enhance treatment requires scientific method. Unfortunately, experiences such as that of Alexander Fleming, who stumbled upon the use of penicillin to treat bacterial infection, are rare.[1] Scientific method involving experimentation on human beings exposes both participant and investigator to risk. The greatest risk of harm and exploitation lies with vulnerable groups, who may be children, prisoners or those lacking mental capacity, as defined by the Mental Capacity Act 2005.[2] A vulnerable population is 'a disadvantaged sub-segment of the community requiring utmost care, specific ancillary considerations and augmented protection in research'.[3] Vulnerability is specific to each study, and is broadly categorized into those patients lacking capacity (or otherwise deprived of autonomy to make informed decisions), and situations exposing participants to coercion. The obvious example in emergency research would involve a patient who is unconscious; however, scenarios where the patient is in extreme pain, delirious or acutely unwell due to hypoxia, hypovolaemia, alcohol or substance misuse must be considered. In these situations, the patient may be unable to understand, retain or debate the information provided and may not be able to verbalize their decision. Emergency care incorporates assessment and treatment of individuals injured or suddenly unwell from the point of contact at the scene to the emergency department; providing life-saving measures in life-threatening situations. Examples would include a cardiac arrest, pedestrian vs. car road traffic accident, status epilepticus and in military cases a gunshot wound, or injuries sustained following improvised explosive device detonation.

In routine practice, as well as the benefit of their clinical experience, clinicians provide pertinent information to patients faced with a treatment decision in order to allow them to make an informed choice. It is this moral obligation that underpins the ethos of ethical research, and maintains the autonomy of participants.[2] Study design has evolved, and we are now seeing research studies

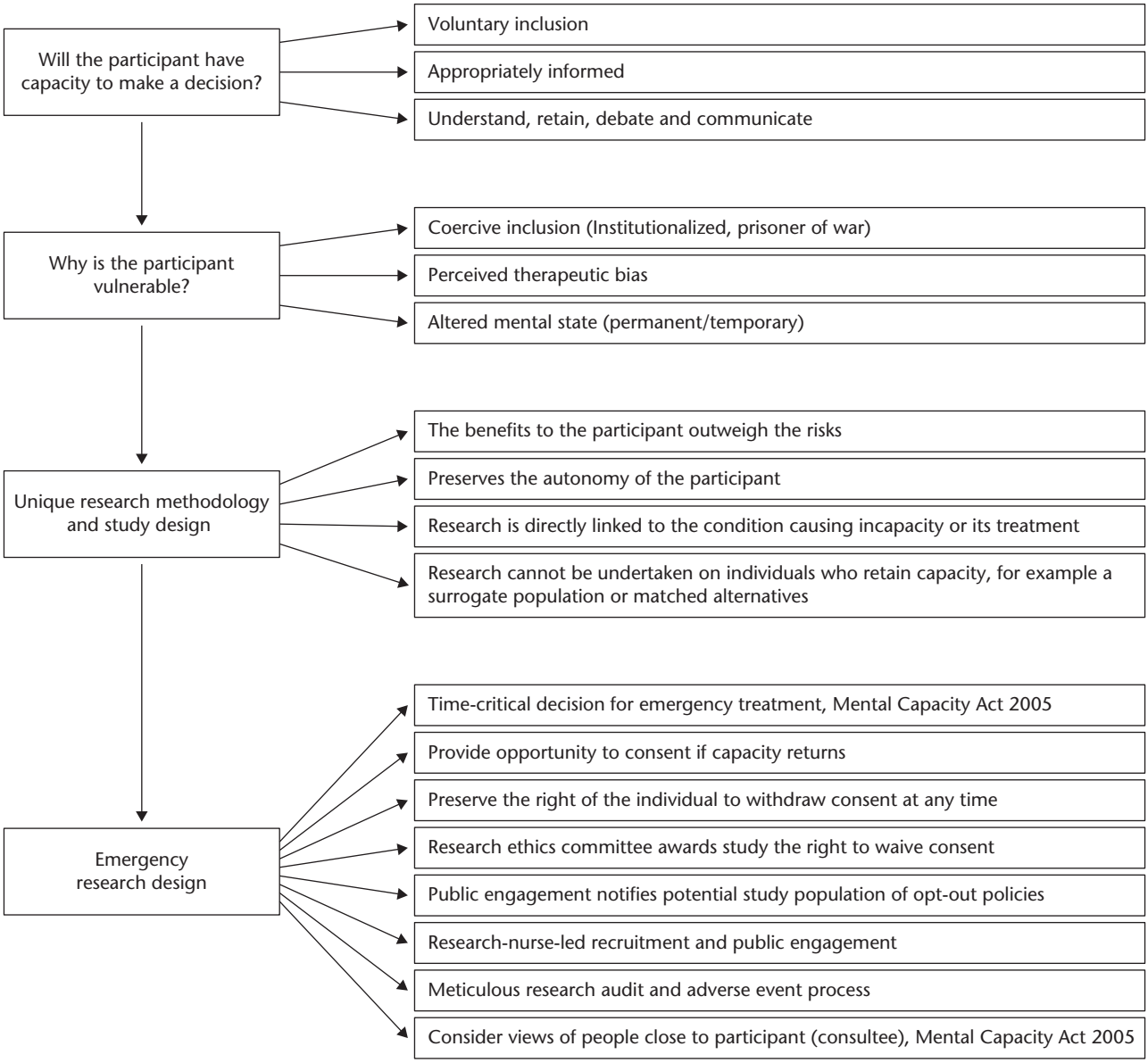

Fig. 1 A schematic illustrating key considerations and process when planning to undertake emergency care research.

embrace the ethical principles of voluntary participation, protection of vulnerable participants and robust research methodology in emergency care of critically ill patients.[4] In this article, we discuss historical events leading to changes in consent procedure, and the development of ethical review boards. We also discuss the pertinent points of current legislation related to emergency care research that define participant recruitment, trial intervention and regulation. Fig. 1 summarizes the key considerations when undertaking emergency research upon vulnerable adult participants.

Informed consent

Maintaining the right to voluntary participation without intimidation, pressure or disadvantage for participants involved in emergency care research is an important obligation for researchers.[5] Time-critical conditions, or altered cognition in acutely unwell patients, can endanger this obligation. In these circumstances it can now be acceptable to enrol these patients without informed consent, provided prior ethical board approval has been obtained. Historically, we have learnt from examples of unethical

research that ignored moral duties and grossly violated human rights. The Nuremburg trials in 1947 exposed the practice in Nazi concentration camps of subjecting prisoners to horrific experiments, purportedly for the betterment of their soldiers, ignoring any principle of voluntary involvement. In response, the Nuremburg directives for human experimentation prompted the World Medical Association (WMA) to implement The Declaration of Helsinki in 1964, which protects research participants and specifically refers to individuals lacking capacity, either due to physical or mental impairment.[6] According to the declaration, the study of unconscious patients may be carried out 'only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group'.[6] This applies to research where capacity has been lost due to injuries causing head trauma, for example during a road traffic accident, or perhaps loss of cardiac output following a myocardial infarction. The declaration accepts greater risk in these vulnerable groups, provided that the research is necessary without alternative methodology (non-vulnerable study population) and has the necessary precautions in place.[6] In emergency research, there is often no alternative group that can be used as a surrogate. Examples in the literature of using surrogate populations in such cases are sparse. However, we identified one particular scenario where experimental findings can be extrapolated across study groups to avoid harming vulnerable participants.[7] Broadly speaking, experience from treating wounded soldiers during operational deployment has been successfully translated into civilian trauma management in the UK. Principles of damage control surgery, evacuation pathways and the early use of specialist doctors, blood products and antibiotics to promptly treat, stabilize and transfer soldiers to higher levels of care have been successfully implemented into UK civilian trauma networks to treat patients with a comparable injury severity score (ISS).

Military personal engaging in combat are made aware of the risks involved with deployment and the potential for recruitment into clinical trials following injury. Consent is this case is implicit. By virtue of the fact that soldiers are serving and deploying, they implicitly accept that they will undergo life-saving surgery if wounded in combat. In Afghanistan, new infantry platoons were routinely escorted around the Camp Bastion Role 3 field hospital to reassure them of the resources available and the high level of care they would receive should they be wounded, as well as to inform them of ongoing research studies aiming to improve patient outcomes. Civilians who may have a similar ISS following high-energy mechanisms, such as those sustained in road traffic accidents, do not have the opportunity to give prior explicit or implicit consent. High-energy trauma requiring damage control surgery, massive transfusion or open fracture treatment is a scenario where surrogate study participants can be used to avoid the potential risk to vulnerable study populations.

Vulnerability can stem from intrinsic causes, where the patient has difficulty in understanding and rationalizing information, and extrinsic causes, which ignore the right to decline participation and invalidate choice.[8] With intrinsic causes, consent can be obtained from a legal representative or waived, provided that it was stated in research protocols and that the study obtained research and ethics committee approval to do so.[9] Recognizing intrinsic loss of capacity is difficult in the emergency department following acute illness, particularly as an individual's capacity can be adversely affected by pain, anxiety and prescribed drugs.[10] In certain scenarios, the patient may be under the influence of alcohol or illicit substances, or simply unconscious due to injury severity. When obtaining consent, the proposed participant must be capable of understanding and weighing risks and benefits, key methodology (randomization, interventions, placebo etc.) and not feel as though they are being coerced, or else disadvantaged when not participating.[5]

Firstly, the ability to comprehend information is dependent upon the patient's reading ability and literacy level, as well as the complexity of the information presented.[11] Secondly, in the emergency department, patients may proceed without a full understanding, perhaps due to a false perception of research representing better care.[12] These mistaken perceptions may be related to an expectation of a reduction in waiting times, superior treatment pathways or preferential treatment by senior doctors.[13] This is often referred to as therapeutic misconception. Flanagan et al describe a correlation between life- threatening injuries and increased susceptibility to therapeutic misconception.[14] Durand-Zaleski et al also found a high prevalence of therapeutic misconception in patients with a greater ISS. Conflict in agenda between investigator and participant can be intensified when the patient perceives a therapeutic advantage.[15] Intrinsic and extrinsic causes of vulnerability, combined with therapeutic misconception, must be addressed in study designs for investigation of acutely injured or unwell patients.

Emergency medicine poses unique challenges to consent compared with elective practice, where time-critical decisions or emergency resuscitation is necessary.[16] In fact, it is often these time-critical interventions that are being investigated. There is often not enough time to liaise with legal representatives to obtain explicit consent, relying instead on exceptions to proceed.[17] Prolonged attempts to obtain consent via a patient or proxy may cause harm, and assessment of incapacity consumes valuable time in dynamic situations.[5] Proxy consent via family or legal authority may not be in line with the patient's wishes if they have not previously specified a caveat regarding involvement in emergency research. If present,

family opinion and support is a valuable resource. However, from the evidence discussed, pre-determined waiving of consent with safeguards to facilitate delayed consent and withdrawal from the programme avoids costly delays in delivery of treatment.[8]

The process of obtaining valid, informed consent is limited by delivery of information, the participants' ability to understand and variance in researchers' practice. When recruiting patients to a trial using a leaflet to advise competent participants, Williams et al found variable comprehension in 82% despite a reading age of above 13 years in all.[18] The leaflet, which was sanctioned by an ethical review board, failed to express pertinent information regarding the trial. When taking participants through the consent process, catering for individual circumstances, range of intellect, or perhaps even language barriers are hurdles most studies strive to overcome. Gigon et al had more success, reporting a higher level of understanding and satisfaction by involving family members in the consent process.[19] Use of technology, such as smartphones, has been trialled with moderate success. Flory and Emanuel found one-to-one consultation to be most effective, endorsing the involvement of research nurses.[20] Emergency research nurses now form the foundations of clinical research, and have been the driving force behind community consultation programmes and public disclosure. These processes engage the public before the start of a trial, and have been used to provide individuals, or groups with similar beliefs, with the opportunity to 'opt out'.[21]

Opting out of a study is an effective safeguard to maintain autonomy in vulnerable groups such as Jehovah's Witnesses, or individuals with particular religious beliefs. It is now common during recruitment, data collection and audit to liaise with a designated research nurse. This has proven to be advantageous in many ways, including extensive community negotiation programmes raising awareness of and identifying vulnerable groups. Specialist research nurses act as an intermediary to lead investigators, as they typically have fewer time constraints on verbal discussion and have access to vast sources of information to draw upon.[22] This avoids perceived coercion by doctors involved in the research programme, and preserves key elements of the doctor–patient relationship.[22] Specialist nurses are crucial to the improvement of medical research, as we are already seeing in the results from recent trials.[23,24] The Control of Major Bleeding After Trauma (COMBAT) study gained approval to perform emergency research in the absence of informed consent, demonstrating the advantages of public disclosure and engagement.[25] It provided special measures for vulnerable patients such as Jehovah's Witnesses and tackled language barriers within the Spanish-speaking population, and their methodology is an example of how difficult research questions can be tackled.

Title 21 of the Code of Federal Regulations governs the Food and Drug Administration of America (FDA).[26] It details the standards for waiving consent, which is permitted with prior institutional review board approval and community consultation. The code faced challenges during its implementation, because review boards were inconsistent in their approvals of study designs.[16] The FDA delegates responsibility to institutional review boards, who evaluate why subjects cannot consent, the urgency and timing of intervention and if there is a reasonable way to predict patients eligible for participation. The code is now established and it is vital that the FDA continues to recognize the need for emergency research, and emphasizes the safeguards required. In 2006, key amendments to UK policy resulted in a broad reflection of the US policy to facilitate emergency research, representing a strategic change from European Union Directive 2001/20/EC, which was not clear on the process of obtaining informed consent in emergency research. The EU Directive 2001/20/EC has since been repealed; with article 35 of Regulation (EU)No. 536/2014 offering clearer guidance to member states on obtaining informed consent in emergency trials.

Study design

The moral objective for research is to innovate and enhance clinical care to benefit participants and the wider community. Any deviation from this ethos undermines the ethics of human experimentation, respect for persons, beneficence and justice.[27] This was the case in the Tuskegee Syphilis Experiment (1932–1972), which was a study of African American men with untreated Syphilis infection, where penicillin was intentionally withheld from participants despite the investigators knowing of its curative effect. Subjects were coerced to participate in the trial with the promise of free medical care, food and burial insurance. Lessons learnt from this event prompted publication of the Belmont Report in 1974, which outlined the ethical principles of research and the need for peer review of study protocols, commonly referred to as the 'institutional review board'.[27]

Reviewers still value these original principles, particularly in vulnerable populations lacking capacity to consent.[28] A 2010 summary of the Belmont Report emphasized seven key components which demonstrate ethical research of the highest quality.[29] For example, it is now mandatory for studies to gain institutional review board approval, which has seen an improvement in trial success and study design. Power calculation is an example of reducing the potential harm and cost of a trial. It calculates the smallest sample size required to gain a meaningful statistical difference between comparative groups. Researchers can cease recruitment into studies when this target sample size is met. This in turn minimizes participant

recruitment, number of interventions and study costs.[28] Naive researchers, reluctant to engage with a review board, increase the risk to subjects and raise the chance of poor-quality results, particularly when continuous research audit and monitoring is neglected. Continuous study audit is important, particularly with multi-centred trials, to allow early detection of harmful interventions and deviation from study protocol by investigators before they jeopardize results.

Within the UK, clinical research or trials are guided by the UK Policy Framework for Health and Social Care Research and Good Clinical Practice (GCP) guidelines.[30] Any deviation from GCP endangers the methodology and results of a study, and negates any legislative protection during negligence claims. Core components of GCP are to protect vulnerable patients, train investigators in research, ensure mandatory waypoints of protocol implementation, auditing practice and policing dissemination of results. Since compliance with the principles of GCP generates reliable results, we can see increasing public trust in the evidence. Unfortunately, it would also be naive to assume that all research today is carried out with complete probity. For example, it took 12 years to retract the study by Wakefield et al, linking childhood vaccination to autism and gastrointestinal disease due to fraudulent activity and conflicting interests.[31]

We acknowledge the unique situations that complicate study design in emergency research, and the industrial-technological advances that drive it. Recognizing this heightened risk, Flanagan et al summarize these scientific and ethical challenges into three broad categories:

1. Designing a rigorously controlled trial that generates useful scientific data, while protecting participants from potential harm.
2. Obtaining informed consent from critically ill patients under conditions of legal and ethical uncertainty.
3. Minimizing the risk of conflict of interest in the face of increased interaction between industry and researchers and their institutions.[14]

Critical care trials are technically challenging to perform, and we typically see high rates of protocol modification or changes to sample size.[32] Emanuel et al also highlight this risk, and advocate the meticulous engagement of independent review and monitoring in order to minimize the effect.[33] However, since 2005, only two-thirds of published trials in emergency medicine have been registered with an ethics committee.[32] The review board can cast an experienced eye over protocols and modify them accordingly. However, we must be realistic and recognize that foreseeing every eventuality is implausible. It is also difficult to differentiate between poor research practice, incompetence and dishonesty. Dishonesty is routinely underestimated within research communities. Fanelli reports that 2% of investigators have falsified results, and overall one-third of investigators admitted poor research practice.[34] Interestingly, one-third of Fanelli's respondents had witnessed fellow researchers falsifying data. Manipulation of data can have devastating outcomes when guiding clinical decisions. The probity issues here degrade the contribution of the patients participating, and risk harm to the wider population where treatment is directed by the conclusions drawn.

A clinician's personal preferences may influence trial outcomes by deviating from agreed methodology, incurring bias in procedure selection and eligibility criteria.[2,35] These preferences may be sourced back to our therapeutic obligation, the Hippocratic Oath, to do the best for our patients irrespective of personal or social obligations.[14] Marquis says that in the absence of clinical equipoise, it would be immoral to randomize patients to a treatment arm that is inferior, or inferior to current standards of care.[36] Marquis also states that randomization abandons the ethical obligations of the doctor–patient relationship. This is particularly the case when it becomes clear that one treatment is superior to the other while the trial continues.[36] Clinical equipoise drives many randomized controlled trials, a scenario of uncertainty that surgeons often find difficult to manage. This may be due to personal beliefs, previous experience or opinions.[35]

For similar reasons, surgeons display cognitive dissonance in recognizing the value of evidence-based research outcomes, but displaying a reluctance to change practice in light of that new evidence. This is particularly common in specialities such as orthopaedics, where surgeons often use a pragmatic approach to treatment decisions based on their own empirical experience and abilities. Historic perceptions hamper the implementation of outcomes from studies, where clinicians critique methodology and results, resisting any subsequent change in practice, even in light of overwhelming evidence.[35] By ignoring dissemination of research, we risk harm to the society we care for. As GCP takes effect, we are beginning to see more robust large-scale, multi-centred randomized trials.[23,37] Although these were initially met with comprehensive criticism, subsequent studies investigating clinical activity suggest a change in behaviour. Costa et al have demonstrated the impact of Level 1 evidence in trauma care.[38]

To maintain public trust, committees must minimize and manage conflicts of interest.[39] A conflict of interest influences judgement sufficiently to align practice for personal or financial gain, disregards the moral obligation to participants, jeopardizes the integrity of a study and poses a threat to society when generalizing results.[40] The incentive for review boards to declare interests and incorporate disclosure into consent processes strengthens research

probity.[41] Patients and research participants have demonstrated naivety towards conflicts of interest, as their inherent trust in science and the medical profession also appears to extend to financial incentives and industry, with little correlation found between disclosures and research participation.[42] Research subjects assume conflicts of interest have been managed by the institution, and it is important we honour that trust.

Modern research utilizes prospectively maintained databases holding confidential patient information. The national Trauma Audit Research Network (TARN) is one example.[43] Individual hospitals also store sensitive patient data for research. The Data Protection Act (1998) regulates the processing of personal data, with the Trust, Health Board or Practice acting as the 'data controller' to determine how and why personal information is processed.[44] Health Services Circular: HSC 1999/012 mandates that each NHS organization in the UK appoint an allocated Caldicott Guardian, a senior person responsible for protecting the confidentiality of patient and service-user information and enabling appropriate information-sharing.[45] During the informed consent process, data handling and storage must also be discussed, detailing the purpose, method and duration of data storage.[5] Patient registries have benefitted orthopaedic care significantly, while national trauma and oncology databases facilitate analysis of large sample sizes to answer pertinent clinical questions. However, there is a vast amount of sensitive data captured and stored which may not be used for its original intended purpose. It is without question that these observational studies add value to patient care; however, we must inform participants of the risks associated with data storage and act responsibly when handling electronic records.

We have briefly explored issues with data storage, dissemination of research findings, conflicts of interest and clinician probity. With acutely ill patients being recruited into clinical trials, the key components and safeguards are community consultation combined with review board scrutiny, methodology that sanctions prospective and retrospective consenting with patient withdrawal upon request, and research audit and monitoring.[46]

Conclusion

Although at increased risk of harm, vulnerable participants have a right to participate in research, and there is often a clinical need to investigate this selection of patients. Failure to do so would both harm potential care advances and advocate the practice of defensive medicine. Attitudes towards research have advanced significantly in the last decade, prioritizing human rights and maintaining autonomy.

There are many barriers to research in the critically ill patient. However, it is acceptable to proceed without consent following appropriate research and ethics approval. To maintain autonomy, proxy consent or delayed consent is good practice, and patients must be given the opportunity to freely withdraw from studies.

Research governance and legislation has been implemented to ensure vigilant protocol methodology to identify and safeguard vulnerable participants. This includes an assessment of the risk–benefit ratio particular to each project, minimizing conflicts of interest, maintaining confidentiality and auditing of research practice supplemented by rigorous training in research education. The major challenge to ethical and effective research remains, perhaps, lack of clinician engagement.

AUTHOR INFORMATION

[1]Health Education West Midlands, Birmingham, UK.
[2]Academic Department of Military Nursing, Birmingham, UK.
[3]Royal Orthopaedic Hospital, Birmingham, UK.

Correspondence should be sent to: Rajpal Nandra, Health Education West Midlands, Birmingham, UK.
Email: rajpalnandra@nhs.net

ICMJE CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest relevant to this work.

FUNDING STATEMENT

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

REFERENCES

1. Fleming A. On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of B. influenzæ. *Br J Exp Pathol* 1929;10:226.

2. Angelos P. Ethical issues of participant recruitment in surgical clinical trials. *Ann Surg Oncol* 2013;20:3184–3187.

3. Shivayogi P. Vulnerable population and methods for their safeguard. *Perspect Clin Res* 2013;4:53–57.

4. Collogan LK, Tuma F, Dolan-Sewell R, Borja S, Fleischman AR. Ethical issues pertaining to research in the aftermath of disaster. *J Trauma Stress* 2004;17:363–372.

5. Nee PA, Griffiths RD. Ethical considerations in accident and emergency research. *Emerg Med J* 2002;19:423–427.

6. World Health Association. Declaration of Helsinki. Ethical principles for medical research involving human subjects. *Bull World Health Org* 2001;79:373–374.

7. Penn-Barwell JG, Roberts SAG, Midwinter MJ, Bishop JRB. Improved survival in UK combat casualties from Iraq and Afghanistan. *J Trauma Acute Care Surg* 2015;78:1014–1020.

8. Silverman H. Protecting vulnerable research subjects in critical care trials: enhancing the informed consent process and recommendations for safeguards. *Ann Intensive Care* 2011;1:8.

9. Miller FG. Clinical research before informed consent. *Kennedy Inst Ethics J* 2014;24: 141–157.

10. Smithline HA, Mader TJ, Crenshaw BJ. Do patients with acute medical conditions have the capacity to give informed consent for emergency medicine research? *Acad Emerg Med* 1999;6:776–780.

11. Montalvo W, Larson E. Participant comprehension of research for which they volunteer: a systematic review. *J Nurs Scholarsh* 2014;46:423–431.

12. Yuval R, Halon DA, Merdler A, et al. Patient comprehension and reaction to participating in a double-blind randomized clinical trial (ISIS-4) in acute myocardial infarction. *Arch Intern Med* 2000;160:1142–1146.

13. Appelbaum PS, Lidz CW, Grisso T. Therapeutic misconception in clinical research: frequency and risk factors. *IRB* 2004;26:1–8.

14. Flanagan BM, Philpott S, Strosberg MA. Protecting participants of clinical trials conducted in the intensive care unit. *J Intensive Care Med* 2011;26:237–249.

15. Durand-Zaleski IS, Alberti C, Durieux P, et al. Informed consent in clinical research in France: assessment and factors associated with therapeutic misconception. *J Med Ethics* 2008;34:e16.

16. Morrison CA, Horwitz IB, Carrick MM. Ethical and legal issues in emergency research: barriers to conducting prospective randomized trials in an emergency setting. *J Surg Res* 2009;157:115–122.

17. El-Menyar A, Asim M, Latifi R, Al-Thani H. Research in emergency and critical care settings: debates, obstacles and solutions. *Sci Eng Ethics* 2015.

18. Williams BF, French JK, White HD; HERO-2 consent substudy investigators. Informed consent during the clinical emergency of acute myocardial infarction (HERO-2 consent substudy): a prospective observational study. *Lancet* 2003;361:918–922.

19. Gigon F, Merlani P, Chenaud C, Ricou B. ICU research: the impact of invasiveness on informed consent. *Intensive Care Med* 2013;39:1282–1289.

20. Flory J, Emanuel E. Interventions to improve research participants' understanding in informed consent for research: a systematic review. *JAMA* 2004;292:1593–1601.

21. Hallstrom AP, Ornato JP, Weisfeldt M, et al; Public Access Defibrillation Trial Investigators. Public-access defibrillation and survival after out-of-hospital cardiac arrest. *N Engl J Med* 2004;351:637–646.

22. Kim SYH, De Vries R, Parnami S, et al. Are therapeutic motivation and having one's own doctor as researcher sources of therapeutic misconception? *J Med Ethics* 2015;41:391–397.

23. Griffin D, Parsons N, Shaw E, et al. Operative versus non-operative treatment for closed, displaced, intra-articular fractures of the calcaneus: randomised controlled trial. *BMJ* 2014;349:g4483.

24. Achten J, Parsons NR, McGuinness KR, Petrou S, Lamb SE, Costa ML. UK Fixation of Distal Tibia Fractures (UK FixDT): protocol for a randomised controlled trial of 'locking' plate fixation versus intramedullary nail fixation in the treatment of adult patients with a displaced fracture of the distal tibia. *BMJ Open* 2015;5:e009162.

25. Chin TL, Moore EE, Coors ME, et al. Exploring ethical conflicts in emergency trauma research: the COMBAT (Control of Major Bleeding after Trauma) study experience. *Surgery* 2015;157:10–19.

26. FDA. *Guidance for institutional review boards: clinical investigators, and sponsors exception from informed consent requirements for emergency research*, 2013:1–64. https://www.fda.gov/media/80554/download (date last accessed 8 December 2019).

27. Parvizi J, Tarity TD, Conner K, Smith JB. Institutional review board approval: why it matters. *J Bone Joint Surg Am* 2007;89:418–426.

28. Vollmer SH, Howard G. Statistical power, the Belmont Report, and the ethics of clinical trials. *Sci Eng Ethics* 2010;16:675–691.

29. Sims JM. A brief review of the Belmont Report. *Dimens Crit Care Nurs* 2010;29:173–174.

30. Department of Health. UK Policy Framework for Health and Social Care Research, 2017. https://www.healthandcareresearch.gov.wales/uploads/Policy%20%26%20Strategy/Research%20Governance/uk-policy-framework-health-social-care-research.pdf (date last accessed 12 March 2018).

31. Godlee F, Smith J, Marcovitch H. Wakefield's article linking MMR vaccine and autism was fraudulent. *BMJ* 2011;342:c7452.

32. Anand V, Scales DC, Parshuram CS, Kavanagh BP. Registration and design alterations of clinical trials in critical care: a cross-sectional observational study. *Intensive Care Med* 2014;40:700–722.

33. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *JAMA* 2000;283:2701–2711.

34. Fanelli D. How many scientists fabricate and falsify research? A systematic review and meta-analysis of survey data. *PLoS One* 2009;4:e5738.

35. Potter S, Mills N, Cawthorn SJ, Donovan J, Blazeby JM. Time to be BRAVE: is educating surgeons the key to unlocking the potential of randomised clinical trials in surgery? A qualitative study. *Trials* 2014;15:80.

36. Marquis D. Leaving therapy to chance. *Hastings Cent Rep* 1983;13:40–47.

37. Rangan A, Handoll H, Brealey S, et al; PROFHER Trial Collaborators. Surgical vs nonsurgical treatment of adults with displaced fractures of the proximal humerus: the PROFHER randomized clinical trial. *JAMA* 2015;313:1037–1047.

38. Costa ML, Jameson SS, Reed MR. Do large pragmatic randomised trials change clinical practice? Assessing the impact of the Distal Radius Acute Fracture Fixation Trial (DRAFFT). *Bone Joint J* 2016;98-B:410–413.

39. Asher SL, Schears RM, Miller CD. Conflicts of interest in human subjects research: special considerations for academic emergency physicians. *Acad Emerg Med* 2011;18:292–296.

40. Solyom AE. Ethical challenges to the integrity of physicians: financial conflicts of interest in clinical research. *Account Res* 2004;11:119–139.

41. Resnik DB. Disclosing conflicts of interest to research subjects: an ethical and legal analysis. *Account Res* 2004;11:141–159.

42. Grady C, Horstmann E, Sussman JS, Hull SC. The limits of disclosure: what research subjects want to know about investigator financial interests. *J Law Med Ethics* 2006;34:592–599, 481.

43. Kehoe A, Smith JE, Edwards A, Yates D, Lecky F. The changing face of major trauma in the UK. *Emerg Med J* 2015;32:911–915.

44. Data Protection Act 1998. https://www.legislation.gov.uk/ukpga/1998/29/contents (date last accessed 25 November 2019).

45. Health Services Circular: HSC 1999/012. https://www.igt.hscic.gov.uk/KnowledgeBaseNew/DH_Health%20Service%20Circular%201999%20012.pdf (date last accessed 25 November 2019).

46. Rincon F, Lee K. Ethical considerations in consenting critically ill patients for bedside clinical care and research. *J Intensive Care Med* 2015;30:141–150.