Ethics in ICU

Critical care research ethics: making the case for non-consensual research in ICU

This presentation is a discussion document to promote knowledge and debate about the issues and ethics of research as they pertain to intensive care medicine. It is based on discussions from a workshop involving intensive care specialists and nurses, surgeons, ethicists, healthcare managers, a lawyer and a biostatistician. Its focus is on participants who were previously fully competent, but are unconscious or otherwise incompetent at the point of decision as to their study inclusion. It is not an attempt to provide a definitive analysis of the issues (i.e. it does not address, for example, research with infant participants, or the legal issues regarding intensive care research): it is an attempt to highlight the major issues.

The clinical significance of critical care research

If non-validated critical care treatments are subjected to the scrutiny of well-designed clinical trials, this can be of major benefit to patients. As well as identifying dangerous or non-beneficial treatments, clinical trials can show that established practice is well grounded or that a new treatment is indeed beneficial. So-called 'established' therapy may simply have acquired such a title for historical reasons and not because this therapy has ever been well-validated by good research (hence the current emphasis on 'evidence-based' medicine to correct such anomalies).

For many years it was widely thought that the haemoglobin in critically ill patients should be kept at a level of at least 10g/L for maximum benefit. A recent trial compared patients who were given a blood transfusion when this level was reached and thereafter maintained at 10 - 12 g/L, with patients transfused only when their haemoglobin dropped below 7 g/L and thereafter maintained at 7 - 9g/L. It was found that the mortality rate was substantially higher in the 'established treatment' group at the higher haemoglobin level.[1] If these results are accurate, and generalisable (and these results are supported by a very recently published study),[2] then hundreds of thousands of intensive care unit patients may have died from unnecessary transfusions.

An even more striking example is the cardiac arrhythmia suppression trial (CAST).[3] It examined the safety and efficacy of certain anti-arrhythmic drugs given routinely to prevent ventricular ectopic beats after acute myocardial infarction as ventricular ectopic beats were known to be associated with higher mortality rate. It was widely assumed that excess deaths were caused by fatal arrhythmias, triggered in turn by the ventricular ectopic beats. In addition, patients entering the trial had already been shown to have their ectopic beats successfully suppressed by one of the trial anti-arrhythmic drugs. The trial randomised patients to receive either a drug of that class or placebo. Many clinicians refused to participate, believing patients in the placebo group were unethically being denied a beneficial treatment. However, it was shown that use of the anti-arrhythmic drugs to prevent ventricular ectopic beats following acute myocardial infarction significantly increased mortality. This effect was so marked that the trial had to be stopped early. Had this trial not proceeded, hundreds of thousands of future patients may well have died.

Treatments may be validated for certain purposes then used for related, but non-validated purposes. The drug etomidate, having been trialled and approved for use as an anaesthetic induction agent, was never trialled in critically ill patients prior to its use for continuous sedation in ICU. After extensive use over several years, a large increase in mortality was reported in one unit.[4] Etomidate was not completely proven to have caused the increase, though animal studies did show a possible mechanism to explain this mortality (e.g. adrenal suppression). If etomidate were the cause, and if a similar increase in mortality rate occurred in other critical care units using the drug, then it can be estimated that, on average, there were 220 additional deaths per 1000 patients treated with this drug. Given that etomidate use had become widespread, this may represent an enormous number of deaths. The problem would undoubtedly have been detected sooner and many deaths probably avoided, if a formal clinical trial had been conducted prior to its use for continuous sedation.

Medical practitioners should offer their patients the most beneficial care they can in light of the best current evidence. Even if harmless, non-validated treatments might not be beneficial or not as beneficial as available alternatives. Their use can also deprive other patients of valuable resources. In short, it is ethically problematic to offer patients non-validated treatments, whether innovative or established. This is a key lesson from the critical care clinical trials discussed above.

Assessing the ethical validity of critical care trials

It is usually recognised by ethics committees (ECs) that research that is scientifically unsound cannot be ethically sound. Any good critical care study will be designed to convincingly answer a research question

that is clear, important and not already answered. Less well recognised, however, is that research must be widely perceived to be scientifically sound by the relevant medical and research communities, otherwise a lack of confidence in its results can seriously undermine its influence on clinical practice. The type of trial that is most widely perceived to be scientifically sound is the randomised controlled trial (RCT) as this design typically has the best potential to minimise bias.

It could be argued, however, that RCTs are inherently ethically unsound. In the ethical evaluation of critical care research, the interests of the enrolling patients are of greater concern than the interests of future patients. Supposing that rather than offering all patients the established treatment for their condition, a critical care clinician enrolls them instead in an RCT where they receive either this treatment or an innovative (or placebo) alternative. If the ensuing trial shows that the established treatment is better, then (so the argument goes) this clinician fails the best interests of those patients randomised to the non-established treatment. Since this sort of outcome is a serious possibility in any well-designed RCT,[6] one might conclude that such trials have ethically unacceptable implications for patients' best interests.

The above argument is dubious. Firstly, its simple contrast between the interests of trial patients and future patients overlooks that trial patients may also be critical care patients in the future. Secondly, the argument holds critical care clinicians and researchers to a super-human 'patient best interests' standard. Specifically, it requires them to always do what in fact turns out best for patients, even if this is beyond the contemporary powers of human understanding and prediction. To confirm that this is unreasonably demanding, consider another case. Here, a critical care clinician refuses to enter any patients into a RCT, and instead offers them only the established treatment for their condition. Other clinicians and patients nevertheless do participate. Suppose the trial subsequently demonstrates that the innovative or placebo alternative is superior to the established treatment. In well-designed RCTs, this result too is always a possibility (as illustrated above by the CAST trial). According to the super-human standard, the clinician here failed the best interests of patients who were offered the established treatment.

A more credible standard of commitment to patients' best interests is needed. The various proposals that have been made, in terms of 'not more than minimal risk', 'benefit to research subjects', and 'appropriate incremental risk',[7-9] rarely make clear the baseline risk or benefit against which they set their standard. This can be addressed by appeal to a standard that is centred on a variant of the familiar idea of clinical equipoise.

On one influential account, clinical equipoise exists when and only when 'there is no consensus within the expert clinical community about the comparative merits of the alternatives'.[10] A more plausible account, however, is that clinical equipoise exists when, and only when, the available evidence to date justifies uncertainty about the comparative merits of the alternatives, whatever the state of clinical consensus. This more plausible account can be read into the following principle. When, and only when, two available alternative treatments (one of which could be placebo, or no treatment at all) are in equipoise, and no third alternative is known to be better, either of the two treatments would fulfil the clinician's duty to patients' best interests. This holds regardless of whether one treatment is later shown to be better. It follows that a clinician or researcher who provides a treatment that best current evidence says is inferior to an available alternative fails this duty. In trial settings, if uncertainty about which of two treatments is better cannot be justified on best current evidence, then randomisation of patients between these treatments fails the duty to patients' best interests.

Returning to the earlier hypothetical examples. In the first, a clinician-researcher randomised patients between established and trial treatments and the former was shown to be better. In the second, a clinician refused to randomise patients, instead offering them only the established treatment, which was then shown to be inferior to the trial treatment. The super-human standard implies that both clinicians failed in their duties to patients' best interests. The 'equipoise standard' implies instead that both fulfilled these duties, if and only if, at the point of decision as to randomisation, the two alternative treatments were in clinical equipoise and that the evidence about the comparative merits of the two was justifiably uncertain. Currently, however there is no universal standard which defines when equipoise exists: given that this uncertainty is inherently present unless proven otherwise the onus should be on proving when equipoise is *not* present. Consensus agreement through professional groups of biostatistical parameters (one example is the minimum number of RCTs and the minimum number of subjects within these trials) required for the standard of non-equipoise to be attained would be one way of reaching a practically useful standard. Such a standard could then be the central focus of EC review of proposed clinical trials.

Clinical equipoise can sometimes cease during long-running RCTs. In particular, interim data collected as the RCT proceeds can sometimes constitute convincing evidence that one treatment is better than the other. Where this might happen, an RCT should be monitored by an independent data and safety monitoring board set up to make informed recommendations as to whether

early trial termination is appropriate.[11] In therapeutic critical care research, appropriate recourse to such a board is a further part of the required commitment to patients' best interests.

Consent to critical care research

Unfortunately, despite their importance to patients, critical care clinical trials have often been unable to generate convincing answers to the questions they set themselves. A recent Cochrane collaboration review concluded that only 4% of trials for the management of head injury were large enough to detect a 10% reduction in mortality. None could detect a 5% reduction.[12] Many, if not most, treatments for head injury remain of unproven efficacy. Difficulties with consent were thought to contribute to problems with recruiting sufficient numbers of patients.

Where a person is able to express her or his will on important matters, the primary function and justification of informed consent is to enable and protect individual autonomous choice'.[13] Individual autonomy is best enabled and protected if consent is freely given or declined by the individual concerned, acting in an informed state of mind, soon before the research or treatment.

When it would otherwise be appropriate to seek their consent to critical care research, many patients are so seriously ill that they are not competent either to give or withhold it. This section first discusses consent issues regarding initial enrolment in a critical care trial, then discusses consent issues regarding continuation of participation. A summary of this discussion is given in table 1.

Consider, first, the minority case of planned or anticipated critical care admission. In some critical care units, post-operative admission from elective cardiac surgery would be such a case. Where the only patients to be included in a critical care study are in this sort of situation, it might well be feasible and desirable to meet the stringent ideal of free and informed prior patient consent.

Even where no particular critical care admission is anticipated, a patient might foresee and address the general possibility. An example is the patient who delegates to another the power to give or withhold consent to medical care or research on her or his behalf, in anticipation of possible future incompetence. Those powers might then be exercised in relevant circumstances in favor of critical care research participation. Delegated consent is a serious consideration in principle, but faces major difficulties in the present setting. One worry is that the act of delegation might not itself be adequately informed. Some might delegate, for example, only because they believe their delegates' decisions would closely

resemble their own. As discussed below, such a belief is often mistaken. Secondly, an evidential difficulty arises over how clinicians can reliably confirm that one person really has freely delegated such a power to another. A third difficulty is that there are often legal restrictions on the freedom of clinicians to recognise such delegations.[14] But the most important difficulty is mundane. In many countries it is rare for individuals to delegate their powers of consent to others, so appeal can only rarely be made to such acts (similar ethical difficulties arise regarding critical care patients who explicitly set out their views in a 'living will' or 'advance directive').

Consider now implicit consent to critical care research. Any actual consent requires a 'positive, intentional act'.[15] Implicit consent can sometimes meet this requirement. Through explicit consent to some things, we do sometimes positively give our implicit consent to others. In explicitly consenting to hospital treatment for serious infection, for example, a patient also typically gives implicit consent to routine monitoring of body temperature. Still, even leaving aside serious evidential questions about its presence or absence in particular cases, implicit consent has little current significance for critical care research ethics. It can exist only where potential critical care patients reliably share the understanding that treatment typically also involves research participation. This is not true of most critical care units. Where it is not true, such understandings would be hard to inculcate. Even if inculcated, they would still not constitute implicit consent to any particular study.

If the only ethically acceptable critical care research proposals are those that fully realise the stringent ideal of free and informed prior patient consent, then a great many important research studies are ruled out, along with all their potential benefits.[16-18] Indeed, several of these studies include important non-consensual elements. Application of the stringent ideal to critical care in general would have even more severe implications. Less demanding consent standards should thus be investigated.

Where no actual patient consent to research is feasible, hypothetical consent might be thought sufficient. This condition is met whenever critical care patients would have consented to participate, were they competently to have imagined themselves to be in their current seriously ill state. For the sake of argument, grant that recognition of hypothetical consent respects the actual agency and autonomy of persons. When, if ever, is it reasonable to judge that the hypothetical consent condition is met?

One option is to judge hypothetical patient consent in light of the views of survivor and support groups. If members of stroke support groups, head injury societies,

Table 1. Summary of Forms of Consent

Competent patient consenting for themselves
Advantages
- best judge of their own best interests
- conditions of autonomous choice can be best upheld
- could be given in anticipation of ICU admission

Disadvantages
- most CC patients cannot meet the conditions of competency at the time of CC trial enrolment
- advance consent could rarely be specific enough to meet standards of being fully informed and hence open for challenge

Implied consent (hospital admission equates with consent)
Advantages
- obviates usual consent procedures at time of admission
- potentially allows greater number of patients to be enrolled

Disadvantages
- requires societal consensus (mandate) and a high level of understanding by patients of general research issues
- unclear if such consent would be mandated for other than very low levels of risk to participants

Hypothetical consent (consent-by-proxy, surrogate consent)
Advantages
- again allows greater numbers of CC patients to participate in research trials

Disadvantages
- requires evidence that patient, if competent, would have consented: no source of such evidence is non-problematic
- generalizing such evidence from therapeutic and/or non-interventional trials to non-therapeutic and/or interventional trials is problematic

No consent
Advantages
- allows greatest number of patient enrollment
- allows greatest number of trials
- reduces consumption of resources (e.g. time) in following consent process
- reduces distress to families in seeking consent at time of admission
- avoids disadvantaging patients who have no family members present

Disadvantages
- potential for conflict between patients' best interests and clinicians' self-interest in the research

Deferred consent
Advantages
- can allow greater numbers of patient enrolment initially
- allows more trials to (at least) commence

Disadvantages
- leads to several forms of statistical bias, some resolvable, some not.

and other relevant groups would typically have wished to be included in such research as part of their own care, this perhaps indicates what current and future critical care patients would consent to. But such evidence should be treated with caution. For example, sample bias arises from the fact that one cannot consult the non-survivors. If more fully researched, the views of such groups would offer some general insight into matters of hypothetical consent, but would not do so for any particular patient.

Another potential source of evidence concerns what patients would have consented to regarding other sorts of non-consensual research. From epidemiological research into public cancer registries, for example, there is evidence that when subsequently explained almost all study participants are comfortable with having been

included without their consent.[6] But here too there are generalisability problems, concerning the reliability of inferences from non-consensual, non-therapeutic and observational research, to conclusions about therapeutic and intervention studies: the evidence regarding hypothetical consent to critical care research is only modest and general.

The most obvious sources of evidence about hypothetical consent are patient nominees and family members but there are difficulties. In one recent study,[19] 16% of patient-nominees judged incorrectly that the patient would have consented to participate in a low-risk therapeutic critical care trial. This 'false-positive' rate rose to 20.3% for consent to participate in a greater-than-minimal risk trial. 'False-negative' rates, where nominees incorrectly judge that the patient would not have consented, were much higher still, at 48.6% and 53.8% respectively. If this study were confirmed by further research, one would have to conclude that patient-nominees are not very reliable. In particular, when their judgment is that the patient would not have consented, it seems they are no more reliable than the toss of a coin. In addition, even self-nominated family members are often unavailable at the relevant time, especially where critical care admission is unanticipated, and treatment decisions are urgent. Overall, then, hypothetical consent seems to be of little help in research ethics.

Some might reply that patient-nominees do much better than chance when they judge that patients would have consented to research. They might add that mistaken claims that patients would consent are much more regrettable than mistaken claims that they would not.[20] It seems arbitrary, however, to claim that patients' decisions and autonomy matter more when they would not participate than when they would participate.

Finally, consider non-consensual enrolment in critical care research. In some cases, this is the only viable research option.[18,21,22] In the United States of America, some cases have been specified by federal regulation.[18,23] If the non-consensual option were pursued, who should determine the matter for each unconscious patient? There are two obvious candidates: clinicians and families. On what grounds should they decide? Since appealing to what the patient would have decided is possibly too unreliable (at least when deciding not to participate), an alternative is to appeal to patient best interests.

Consider the claim that only families should decide non-consensual critical care research involvement, grounding such decisions in their assessment of patient best interests. This approach has been widely pursued in critical care settings. Difficulties arise, however, for all involved. Relatives can find it confusing and distressing at the time of unexpected critical care admission to have

to make such decisions. Their subsequent recollection and understanding of the research can be minimal, even when a good decision process is carefully followed. Intensivists can find the process distressing too. These factors have perhaps reduced patient enrolment in clinical trials that rely on family decision. In the United States of America at least, 'family decision' policies have also tended to reduce participation from lower socio-economic groups, whose families are less often immediately available. This reduces their access to the benefits of research,[24] in part by adversely affecting the generalisation of study results to such groups. Non-availability of family members at the key time is also a serious general problem at unexpected critical care admission. Even when family members are available, the urgency of the clinical situation can make any informed family decision non-feasible. Apart from all these things, it can also be difficult for clinicians to determine quickly that they are accepting the 'family decision' of the appropriate person(s). This remains so even where all those present appear to be 'family', all family seem to be present, and they all agree on the matter.

Consider now the claim that only clinicians should make decisions about non-consensual research involvement, grounding these in their assessment of patient best interests. One worry here is that clinician-researchers might sometimes face conflicts between their patients' interests and their own research interests. Such conflicts can be mitigated by involving, where feasible, clinicians who are not also study researchers, and by consulting with families. Family decision-making too is vulnerable to many conflicts of interest. Concerns remain, however, as to the adequacy with which clinicians can identify and appreciate the individual patient values which weight any scientific facts, and thus the adequacy of this process to define patient best interests.

Deferred consent and the problems of withdrawing from trials

One strategy to avoid the above difficulties has been the development of obtaining patient consent after they have become competent to do so (variously termed 'retrospective approval'[25] or 'deferred consent'[26]). Patients in critical care studies can be offered this option, together with the option to withdraw entirely, and (where relevant) the further option to withdraw from their allocated treatment whilst leaving their data in the trial. Both of these options hold a number of implications for the scientific and ethical validity of the research, even in RCTs.

Firstly, withdrawal of a critical care patient from a study can reduce the generalisability of the research, reducing the likelihood it will generate results

convincing enough to confirm or refute the research question. Withdrawal of any patient also has implications for all the other remaining patients in the study as well as those of future patients. Those continuing in the study will still face the same risks but with fewer benefits. These matters should be addressed at initial patient enrolment, so all decision-makers know the implications that later withdrawal would have for themselves and for others. If those patients likely to stay in the study can be identified in advance, then enrolment can perhaps be sought only from them. Even if there are consequently fewer enrolments, this is preferable to having large numbers of withdrawals. It preserves the scientific integrity of the study, though at some cost to generalisability.

If self-withdrawal is offered, this can be taken up only by those who regain sufficient competence soon enough. This causes problems of bias and of generalisability to sicker patients. For example, if more patients in the study group improve than in the control group but many of those who improve withdraw from the study, this could lead to an incorrect conclusion that the study treatment is of no benefit. Conversely, if more patients in the control group improve but some withdraw, this could lead to an incorrect conclusion that the study treatment is safe (or possibly even beneficial) when in fact it is harmful.

Surrogate decision-makers might also be offered the option of withdrawal on behalf of enrolled relatives. Surrogates of the most ill patients, or of those who fail to improve following treatment, might be especially inclined to take this option. This again would mean that the study's results could be biased, and might not be generalisable to the more critically ill patients, who might most need research-based knowledge. Similar difficulty is caused by any EC requirement that investigators seek prior to hospital discharge, consent for continuing follow-up from those CC study patients who recover sufficiently to leave hospital. This has been an issue, for example, in the CRASH trial.[18] This has real possibilities of bias and of studies generating mistaken conclusions regarding therapy safety or efficacy.[27] If there are unrecognised variations between the circumstances of those who continue and those who withdraw, or between those asked for their consent to follow-up and those not asked, trial results are likely to be misleading if applied to the whole study population. In general, if the characteristics of those who withdraw differ in any way between the treatment and control groups, the results are likely to be significantly biased.

Return now to the idea that a patient's withdrawal from a trial might be from treatment only, leaving her or his data in the study. If critical care treatment is ongoing, this option has considerable advantages over complete withdrawal. Intention-to-treat analysis can be

carried out to cope with patients' withdrawal from their allocated treatment, although if a high proportion of patients opts for treatment-only withdrawal even this might underestimate a true treatment effect. Some ECs might worry that even to mention the option of treatment-only withdrawal is to pressure participants not to withdraw. Yet failure to mention it compromises participants' autonomy, by denying them an option that some might well prefer over any other. It also overlooks the important interests other patients have in the matter, both current trial participants and future patients. Although certain statistical tests can compensate sometimes for problems of bias and generalisability, this is not always possible especially if the treatment gains are only modest. This requires knowledge and information regarding prognostic factors for the disease outcome to a level of accuracy that is generally unavailable. The need to use such techniques itself also has an unfavourable affect on trial credibility. Critical care studies must be generalisable and not significantly biased. If a trial is weak on either count, this can delay its completion, and thus potentially the transfer of its in-trial patients from a less beneficial to a more beneficial treatment. It can also delay the wider improvement of clinical practice, in effect by subjecting yet more patients, here or elsewhere, to further iterations of much the same clinical trial processes and ethical difficulties. In short, all parties have an interest in high quality critical care studies.

Community acceptance of intensive care research

It was argued above that a critical care study is ethically acceptable only if worthwhile, and worthwhile only if likely to answer convincingly a research question that is clear, important, and as yet unanswered. It is important to the viability, and thus also the social value and the ethics of trials that they meet these conditions right through to their completion. If key groups are not 'on side', it is likely that important issues have not been adequately addressed, leaving the critical care studies themselves vulnerable to controversies that might derail them. More generally, it is important to maintain good researcher-community relationships, and to strengthen community trust in researchers and research.

The key groups discussed briefly below are patients, their relatives, patient survivor groups, and the community at large. Other key groups include critical care professionals and ECs.

The advisory committee on human radiation experiments (ACHRE),[28] has suggested that many patients, especially those with a poor prognosis, participate in research because they believe it is the best way to improve their medical condition. ACHRE argues that the possibility of benefit from research tends to be magnified by both participant and researcher, and this

might seem to raise doubts about whether such patient consent is adequately informed or free. On the other hand, there is now significant evidence of an 'inclusion benefit' in therapeutic research – 'a benefit that accrues to patients simply by being included in a research protocol'.[29,30] If well-designed therapeutic critical care research confers this benefit on patients, in addition to any benefit arising from the therapy itself, then patients might well be correct, instead of over-optimistic, to think their participation is likely to benefit them.

One study,[31] investigated the views of research held by relatives of 200 Canadian critical care patients. All believed that critical care research is useful, but most were wary of patient enrolment without any relative's permission. They regarded spouses and parents as highly acceptable sources of proxy consent or substituted decision-making.

Legal options such as the power of attorney or advance directive were less well regarded. Their acceptance of research also reduced as severity of illness increased. Care is nevertheless needed regarding these findings. It is uncertain, for example, whether respondents knew how important for patients themselves the results of worthwhile critical care research can be, or understood the difficulties that substituted decision-making processes can cause.

Many patient survivor groups set up research programs in their interest areas, or actively support research in other ways. In critical care settings, relevant groups include stroke support groups and head injury societies. Their attitude to CC research has unfortunately been little investigated to date.

In Britain at least, the wider community is broadly supportive of medical research.[32] This study also showed that the general public can understand complex distinctions between different types of research, and can grasp underlying ethical issues. Positive public attitudes towards medical research might well generalise to critical care research, but this is uncertain.

Focus group discussion in community settings can inform and sometimes change community-held views about medicine.[33] Recently, a paper described how the involvement of consumer groups facilitated the design of the consent procedures for an RCT concerning the treatment of stroke;[34] this suggests that, if given opportunities to participate in informed discussion of the issues, relatives and other key communities might develop a greater sympathy toward other forms of critical care research, including non-consensual studies where needed. In particular, if community groups were more aware of the extent of the harm that is sometimes caused by failure to validate treatments through systematic research, then their level of support for critical care research might well be high.

Conclusions

Critical care patients are very ill. Even small gains in our knowledge of treatment safety or benefit can make a life-saving difference to them. Partly because these patients are so ill, however, many established treatments are poorly validated. These might be less beneficial than other options, not beneficial at all, or even fatally harmful to patients. Critical care professionals, their patients, patients' families, ECs, and wider communities consequently have strong reason to support well-designed therapeutic research.

The serious illnesses of critical care patients often make informed patient consent difficult or impossible, yet recourse to delegated consent, implicit consent, hypothetical consent, or family decision-making is problematic. Important among the diverse problems here is the fact that these non-ideal consent processes tend to bias and to undermine the generalisability of intensive care research findings. This can cost patients their lives. In this light, researchers and ECs are encouraged to sympathetically consider the overall merits of non-consensual intensive care research when the patient is unable to consent. Non-consensual does not mean uninformed: adequately communicating and informing participants and their families about these complex issues is a difficult but necessary part of good research.

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