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CLINICAL COMMENTARY

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Is it better to consent to an RCT or to care?

Μηδεν αγαν ("nothing in excess")

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Μηδεν αγαν ("nothing in excess"): this famous motto of the Delphi oracle is inscribed on the temple of Apollo (http://www.wordiq.com/definition/Delphi).

I have no conflict of interest to declare. My taking into account of positions expressed by the Alliance for Human Research Protection does not mean that I endorse all the opinions voiced by this organization, of which I am aware via its website only.

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Introduction

Twenty-five years ago the Belmont report [1] established a formal distinction between care and research in order to protect patients. The legitimate fear that research might be conducted under the pretence of medical care regardless of whether this increased the risk to patients drove this effort toward clarification. A sound ethical foundation to medical research was deemed essential after the heinous Nazi experiments and the abhorrent 40-year-long Tuskegee syphilis study [2]. At the time that the Belmont report was issued randomized clinical trials (RCTs) were coming into vogue. An RCT is not routine clinical care, even when the treatments in both study arms are consonant with standard practice. Thus both the ability of RCTs to produce high-quality medical knowledge and the distinction between care and research were considered of paramount importance at the time of the Belmont report [1]. Whether research should be incorporated into medical care remains controversial, however, as reflected by several recent and conflicting statements of opinion [3, 4, 5].

I argue here that things have changed since the Belmont report, and that a formal distinction between care and research may no longer serve medical or ethical principles in many situations, most notably in the area of critical care. This seemingly provocative position stems from three arguments. First, a large part of the "research" conducted in ICU patients consists in evaluating practices or comparing two widely used procedures or treatments [5]. Second, the scientific value and the historical role of RCTs may have been overemphasized and their socioeconomic impact misinterpreted. Third, analysis of the informed consent process, a mandatory preliminary intended to ensure the autonomy of patients included in RCTs, suggests that the cure may be worse than the disease. Although informed consent was a major stride towards protecting the rights and dignity of patients, the process may in some instances be perverted into protecting the physicians rather than the patients. The tragic Jesse Gellsinger case ("Teen dies undergoing experimental gene therapy," *Washington Post*, 29 September 1999) reminds us that "informed consent" is not sufficient to protect patients during research [6]. The informed consent process has many flaws stemming from the frequent complexity of consent forms [7], poor comprehension of information by many families who must draw on their limited scientific culture to unravel complicated issues at a time when they are struggling with severe anxiety about their loved one [8], and dearth of communication skills among physicians. Thus, informed consent to research may be stressful for families and reassuring for physicians. This was not its original purpose.

To overcome these problems a reform allowing informed consent to be waived under specific circumstances has been suggested [5]. Although the opinions expressed by the advocates of this approach are worthy of respect, they conflict with the principle of patient autonomy [9]. A similar wish is expressed by some European physicians who seem very anxious about the putative threat on medical research in emergency that a new European Directive supposedly poses [10, 11, 12]. Indeed, this Directive [13] does not allow the waiving of consent by proxies.

Another contention of the present paper is this [14]: critical care physicians may still believe that RCTs remain the best tool for improving knowledge and care, and in this case they must accept to use the means needed to achieve the end and therefore to insist on mandatory informed consent from the patient or proxy; or they may realize that the game is not worth the candle and they must then turn to other forms of research that are ranked less highly in the pyramid of evidence-based medicine [15]. In so doing they give priority to the well-being of families and must seek the help of innovative methodologists who accept to deal with the real world.

Before discussing the problem of informed consent to research a critical appraisal of the scientific and ethical validity of RCTs in critical care medicine is in order.

The role of RCTs was overemphasized from the outset

Many critical care physicians believe in the superiority of RCTs over other types of clinical studies. This belief may not be supported by the evidence. Before discussing objective data on the value of RCTs in critically ill patients it is important to recall a number of historical facts.

RCTs emerged in the 1940s as a tool for overcoming the drawbacks of anecdotal experience. Although RCTs initially met with considerable resistance, they undoubtedly contributed to making clinicians aware of the need for rigorous methods. However, the data obtained proved only that RCTs are feasible, not that they are superior over other forms of well-conducted studies. This is best illustrated by the trials of streptomycin in tuberculosis in the United Kingdom and of the Salk polio vaccine in the United States. Streptomycin was discovered in 1944 in the United States. The British government could not afford to purchase streptomycin for all patients with tuberculosis, and the effectiveness of the drug was not yet established. The words of D'Arcy Hart [16], a member of the Medical Research Council scientific staff that conducted the streptomycin trial, are worth quoting: "The trial proceeded from 1947. The small amount of streptomycin available made it ethically permissible for the control subjects to be untreated by the drug—a statistician's dream."

This gives the two reasons for the trial: fair allocation of a limited resource and the determination of a brilliant statistician, Sir Austin Bradford Hill, to prove the validity of RCTs. D'Arcy Hart [16] further stated: "Secondly, the trial heralded the general conversion of clinical scientists to randomisation." Shortly after this brilliant demonstration of the feasibility of RCTs the Salk polio vaccine trial was interpreted as a triumph of the new RCT method in the United States. The unique circumstances surrounding the vaccine trial deserve mention [17]: There was a raging scientific controversy between Salk and Sabin regarding the type of vaccine that should be developed (Salk was developing a killed virus vaccine, whereas Sabin thought that only an attenuated living strain could be a suitable vaccine), and Salk was under considerable pressure to perform the trial, both to stop the polio epidemic that was costing so many lives among children and to win the race against Sabin. For the trial children in a number of states were randomly allocated to receive the vaccine or a placebo. The results proved the vaccine dramatically effective. This both improved medical care and propelled the RCT to prominence as the gold standard design for clinical research. However, an observational study was conducted in states that refused the placebo-controlled trial [17]. The results were similar to those of the RCT, but only the results from the RCT were considered statistically valid [18]. Interestingly, Salk described the placebo-controlled study of his vaccine as "a beautiful... experiment over which the epidemiologist could become quite ecstatic but (which) would make the humanitarian shudder" [17]. It seems that this RCT was driven by statisticians rather than by clinicians, in order to counter Sabin's criticism and gain the support of the leaders of the medical community [17].

In brief, RCTs were performed because they could be performed, not because they had been proved superior over other study designs. The same may still hold true in critical care research today.

What is the socioeconomic role of RCTs?

Henry K. Beecher, a professor in anesthesia research at the Massachusetts General Hospital commenting 40 years ago on the huge increase in funds for research, said "There is reason to fear that... these resources may be greater than the supply of responsible investigators," and "Every young man knows that he will never be promoted to a tenure post, to a professorship in a major medical school, unless he has proved himself as an investigator" [19]. These two sentences acknowledge an uncomfortable reality: money and careers are at the center of clinical research.

The importance of RCTs for drug companies

Large RCTs are vital for drug companies. These trials are mandatory not only for proving the efficacy of new products but also for obtaining regulatory approval and marketing licenses for drugs. Thus drug companies have good reason to argue that RCTs offer unequalled methodological purity. However, drug company sponsored trials of both hematology treatments and nonsteroidal anti-inflammatory drugs usually showed superiority of the new drug [20]. This finding obviously violates the principle of equipoise, under which one would expect only one-half of the studies to find better outcomes with the new drug [20]. A similar bias has been reported with other studies funded by the pharmaceutical industry and ascribed to the use of an inappropriate comparator or to publication bias [21].

The importance of RCTs for medical journals

Although the editors of major medical journals have recently warned against the threat to objectivity posed by some forms of industry-sponsored research [22] and stated that "the use of clinical trials primarily for marketing makes a mockery of clinical investigation," the potential for disseminating pharmacological breakthroughs makes them likely to accept most of the industry-sponsored trials. The recent controversy on the efficacy and safety of activated protein C in sepsis highlights the difficulties faced by editors in this area [23, 24]. The ties that link drug companies to investigators and to prestigious academic centers pose a worrisome threat to academic medicine [25]. Money from advertising may also weigh on editorial policies.

The importance of the power of methodologists

Methodologists and statisticians are consulted by drug companies and by independent investigators at the study-design stage and by editors at the peer-review stage. They developed the rules of "methodological validity," and these rules are likely to be the same at each step of the design and publication of a clinical trial. The grading system for the quality of evidence from clinical research, with RCTs at the top, is akin to a self-fulfilling prophecy: young researchers and renowned experts alike comply with these "golden" rules to ensure publication of their findings in a prestigious journal. This compliance with artificial rules is taken as firm evidence of validity, thus spinning the wheel endlessly. As stated by Knottnerus and Dinant [26], "Finally, in using strict criteria in reviewing manuscripts for publication, we should worry about risk avoidance by clinical researchers. They might focus their energies on topics where the methodological criteria of reviewers and editors can be most easily met, rather than studying real life clinical problems which present substantial methodological problems." The adage "publish or perish" still applies.

All these interests shared by drug companies, investigators, methodologists, and journals concur both to overproduction of RCTs and to overestimation of their contribution to medical progress. RCTs tend to become an uncontrolled activity driven by forces foreign to scientific goals. This results in an inextricable tangle of so-called evidence. Then, meta-analyses are performed, supposedly to clarify an issue that has been artificially obscured. They may merely add to the confusion, as discussed below.

How useful are RCTs in critically ill patients?

The validity of conclusions of earlier studies on hepatitis and cirrhosis has been evaluated by Poynard and coworkers [27] under the provocative title of "Truth survival in clinical research: an evidence-based requiem." In this study the 20-year survival rate of conclusions derived from meta-analyses was lower (57%) than that from nonrandomized studies (87%) or RCTs (85%). More importantly, the truth survival rate was similar for studies of high and low methodological quality.

Examination of three important areas of critical care further indicates that challenging the usefulness of RCTs is not necessarily sacrilegious. The acrimony of the debate on these three topics in medical journals and at international meetings is a strong indicator that RCTs fail to provide the "definitive" answer expected from them. These three topics are mechanical ventilation in adult respiratory distress syndrome (ARDS), selective digestive decontamination (SDD), and prevention of gastrointestinal bleeding.

Mechanical ventilation in ARDS

Controversy erupted after publication of the findings of the ARDS Network study on tidal volume reduction during ARDS. Although this remarkable work showed that a low tidal volume of 6 ml/kg predicted body weight resulted in better outcomes than a higher tidal volume of 12 ml/kg [28], it did not tell us how to ventilate these patients. Decreases in mortality [29] and tidal volume [30] over time occurred well before the study was initiated. Patients are usually ventilated with tidal volumes that are intermediate between the two arms of the ARDS Network trial (and probably closer to the lower volume). There is no RCT telling us whether 6 ml/kg is better than the 8–9 ml/kg generally reported in international surveys [31, 32]. The results of this trial will encourage clinicians to use smaller tidal volumes, a practice that has not yet gained sufficient acceptance [33, 34, 35]. In that sense

this RCT will prove useful, but not more useful than the earlier experimental, physiological, and nonrandomized clinical trials that resulted in the use of gradually decreasing tidal volumes over time [30]. It is merely one more brick in the wall, and not a gold one. Similarly, the results of the recent ALVEOLI randomized study that compared two PEEP levels will probably not change current practice [36]. In this study PEEP levels higher than the moderate values used in most surveys [31, 32] did not improve patient mortality. Finally, will the lack of effect of prone positioning on mortality in RCTs [37] discourage clinicians from using this very inexpensive and effective maneuver to improve patient oxygenation, and will these clinicians continue to await an RCT providing "proof" of efficacy [30]? ARDS mortality rates have decreased substantially over the years [29] and are probably declining further still, yet this improvement is ascribable not to RCTs but to patient-oriented research based on sound physiological thinking [30, 38, 39, 40].

Selective digestive decontamination

Meta-analyses of RCTs indicate a clear survival advantage with SDD [41, 42]. However, SDD is seldom used because of the legitimate fear that this practice may promote the emergence of resistant bacteria [43, 44]. How many studies will be needed to convince clinicians to use a method they do not want to use? Or shall we wait until the "final" meta-analysis is "negative" and "proves" that clinicians were right when they refused to use SDD despite the accumulation of so-called evidence?

Prevention of gastrointestinal bleeding

Few fields in critical care have generated as many RCTs and meta-analyses. A recent meta-analysis concluded that sucralfate and ranitidine failed to prevent gastrointestinal bleeding in critically ill patients [45]. The authors noted that a previous meta-analysis [46] found reduced bleeding rates with H_2 antagonists but included several positive trials of cimetidine, which has since then been superseded by drugs with better safety profiles. In addition, the use of proton-pump inhibitors seems to be increasing in critically ill patients, although there is no proof that this practice is beneficial. Finally, no one knows whether prophylaxis should be given, and this uncertainty has recently been exacerbated by an observational study in 1,400 patients showing no difference in bleeding rates between a cohort of patients given prophylaxis and a subsequent cohort not given prophylaxis at the same institution [47]. Additional RCTs may be needed if the obsessive goal is to discover the illusive "truth," but their drawbacks should be weighed against their utility.

What methodological problems do RCTs pose in critically ill patients?

This paper does not claim that all RCTs are useless in critically ill patients. RCTs may be helpful for evaluating a single and simple intervention (even if this intervention is technologically sophisticated) in patients with a well-defined disease. This is obviously the case for acute coronary syndromes. However, many conditions seen in ICU patients stem from extraordinarily complex pathophysiological mechanisms that preclude simple trial designs and interpretations [30]. A typical example is the patient with ARDS and septic shock, multiple indwelling catheters, and a high risk of nosocomial respiratory and systemic infections. It is difficult to conceive of a single therapeutic intervention capable of improving such a complex situation. A further obstacle to studies on such an intervention is the highly heterogeneous nature of the ICU population. These issues relate to the internal and external validity of a trial. Methodologists seek to maximize the internal validity of RCTs to decrease the effects of confounders. However, as internal validity increases, external validity (i.e., generalizability) decreases [26]. This problem may exist for the ARDS Network trial on tidal volume reduction [28]. Indeed, because extremely stringent inclusion criteria were used, only 10% of ARDS patients admitted to the participating centers were included in the trial [48].

What ethical problems do RCTs raise in critically ill patients?

Some RCTs may conflict with currently accepted principles of medical ethics [49]: beneficence, nonmaleficence, autonomy, and justice [1, 50]. In addition, RCTs may conflict with the principle that what is not scientific is not ethical.

Beneficence and nonmaleficence

It is of course difficult if not impossible to determine a priori that a research protocol has a favorable risk-benefit ratio. However, RCTs should rest on a foundation of strong experimental or clinical concepts. This may not have been the case in all instances, most notably in studies of new treatments for sepsis [51]. Without seeking to fuel the debate on the failure of antimediator agents in sepsis, one cannot but wonder whether the huge financial and academic stakes were in part responsible for the apparent haste with which some trials were conducted. In addition, the quality of research oversight in several trials with high mortality rates has been challenged [52]. It is difficult to ensure that the prerequisites for beneficence and nonmaleficence are met when there is a major influence of

financial incentives and academic competition. Thus we still encounter problems similar to those met by the Salk vaccine trial: The process of virus inactivation was not fully mastered at all the vaccine production sites, and therefore active virus was inoculated into a number of children in whom poliomyelitis developed (http://www.pbs.org/wgbh/aso/databank/entries/dm52sa.html, accessed 19 July 2004; http://www.polio-vaccine.com/fr/histoire/vaccins_experience.html, accessed 19 July 2004). Another aspect of beneficence and nonmaleficence that does not seem well addressed during the conduct of RCTs concerns proxies and are discussed below.

Autonomy

Most critically ill patients are too ill to deal with issues of consent. Consent is therefore sought from a surrogate in the United States and most European countries. Consent by a surrogate is usually considered the best means of protecting patients during research [53, 54], although studies have shown that the decisions made by surrogates do not always reflect the wishes of patients [53, 55]. However, some states in the United States either do not accept surrogate consent for research or authorized this form of consent only after the end of the ARDS Network study [56]. In addition, mistrust is gaining ground in the public at large, and organizations such as the Alliance for Human Research Protection (AHRP), whose stated goal is to ensure that human rights are protected during research (http://www.researchprotection.org, accessed 19 July 2004), are opposed to surrogate consent. The AHRP contributed to drive the inquiry of the Office for Human Research Protection on the ARDS Network trials [57]. Surrendering the principle of autonomy to the principle of beneficence is ethically acceptable only when there is a reasonable certainty of nonmaleficence. This degree of certainty is not usually obtainable, as discussed above.

Justice

Tremendous amounts of money are invested in clinical research, in principle in the best interest of patients. The above words of Beecher [19] on the discrepancy between the abundance of funds and the scarcity of responsible investigators deserve careful consideration. Financial resources for healthcare and for research are limited [58], and their fair allocation is both a political and an ethical imperative. Because RCTs are far more expensive than observational studies [59], they should provide answers that cannot be given by observational studies. Although the impressive work conducted by the ARDS Network investigators is worthy of respect, its failure to achieve this goal must be acknowledged. Millions of dollars were spent [60], but, as discussed above, this study [28] is merely one among several (including physiological and observational studies [30]) showing that patients should be ventilated with less than 10 ml/kg body weight. In addition, it failed to determine whether volumes smaller than the 8–9 ml/kg noted in observational studies should be used [31, 32]. Similarly, the ALVEOLI trial [36] randomized a large number of patients but simply ruled out a need for PEEP levels higher than those in observational studies [31, 32]. What have these multimillion-dollar trials contributed?

Science

In the words of the Belmont report [1], "The term 'research' designates an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge." It is usually assumed that a nonscientific trial is unethical. But how generalizable are the data generated by RCTs with excellent internal validity but limited external validity? As mentioned above, what makes the greatest contribution to clinical practice regarding the prevention of gastrointestinal bleeding in ICU patients: "discordant" meta-analyses of multiple RCTs [45, 46] or a well conducted cohort study [47]?

The informed consent dilemma

This is a major ethical issue. As brilliantly discussed by several authors, informed consent by a proxy is a key safeguard for patients eligible for clinical trial inclusion [6, 53, 54]. However, proxies may not consistently make the same choices as the patients or correctly interpret their best interests. In addition, the consent process can impose considerable suffering on the proxy. However, investigators are encouraged to disseminate the results of their work to the study participants [61], which is laudable. After the death of a loved one, a proxy might learn, for instance, that he or she consented to a clinical trial in which mortality was higher in the treatment arm. In that sense informed consent probably protects the ICU patient and the physician in charge of the research project but not the proxy who is asked to provide consent. Anxiety in patients asked to give their "full informed consent" to a study of a life-threatening disease has received attention [62]. It has been rightly pointed out that this form of consent may be needlessly cruel [63]. The same may hold true of "full informed consent" given by a proxy for a loved one. Everyday practice teaches that proxies are highly vulnerable to distress and guilt when they are asked to provide consent to care for a critically ill patient (e.g., to a high-risk therapeutic procedure in a desperately ill patient). Families of ICU patients often exhibit major signs of anxiety and depression [8]. The information that

they receive in the name of the principle of autonomy may conflict with the principles of beneficence and nonmaleficence when proxies are asked to consent to research rather than to care. The primary focus of informed consent is risk disclosure [64], and the informed consent dilemma can be summarized as follows: If the consent form is to be reassuring for the family, it must fall short of providing honest information, and if the consent form is to be honest, as commendably proposed by the ARDS Network investigators [65], it must supply information that is distressing to the family. Surprisingly, most physicians fail to recognize that evaluation of the risk-benefit ratio, considered a requisite for ethical research [6], should not focus solely on the patient. The emotional risk to proxies should be balanced against the putative benefit (and risk) for the patient included in the RCT [14]. Otherwise, proxies may be subjected to stress whose harmful effects exceed by far the objective benefits the patient may derive from participating in the study. Does it make ethical sense to distress family members by asking them to consent to yet another study on SDD or on the prevention of gastrointestinal bleeding? Informed consent documents and information sites for families of critically ill patients are sometimes so frightening that perhaps the door to the ICU should bear the words inscribed on the gate to Hell in Dante Alighieri's *Inferno* (La Divina Commedia): "Lasciate ogni speranza, voi ch'entrate!" ("Abandon all hope, ye who enter here!").

Potential solutions

Two categories of solutions may be considered. Some require no important qualitative changes in the system that governs clinical research but simply a tightening of research oversight procedures [53, 66, 67]. Other solutions would require a reshaping of many parts of the system, including the financial and academic incentives to publication, as well as a number of methodological dogmas. These two categories of solutions are not mutually exclusive. They both seek the best compromise between conflicting principles to protect the rights of patients and proxies and to improve scientific knowledge and quality of care, but not at the expense of scientific or ethical distortions.

Solutions that do not require significant changes in the system

Waiving of consent for research in emergencies

The protection of subjects who are unable to give or refuse consent must receive particularly close attention. There is little doubt that waiving of the requirement for consent should be reserved for highly unusual situations [53], which are described in detail in the United States Code of Federal Regulations for the Protection of Human Subjects [68]. This text allows some forms of research in emergency situations without consent from the patient or surrogate provided certain conditions are met, including: the disorder is immediately life-threatening, available treatments are unsatisfactory, obtaining consent is not feasible, the research could not be carried out without the waiver, participation in the study holds the prospect of direct benefit, and the waiver of consent is given by an institutional review board. The situation is less clear in Europe where research in emergency medicine can be performed without consent in some countries (including France) but not in others [11]. However, the European Parliament and Council have issued a new Directive that forbids research without consent, even in emergencies [13]. This Directive has been criticized as a serious potential threat to research in emergency situations [10, 11, 12, 69]. Before examining the magnitude of this threat, one must acknowledge the risk of overuse or abuse of waiving consent for emergency research in critically ill patients [14, 70]. As recently argued by John Luce, "few patients face true emergencies.... For example... studies of new modes of mechanical ventilation, novel therapies for sepsis... have a relatively long therapeutic window during which obtaining consent from patients or surrogates may be possible" [53]. For research on true emergencies (e.g., treatment of cardiac arrest, acute brain injury) in the European Union the Directive and/or the research modalities will have to be modified, as discussed below.

Waiver of consent for selected randomized controlled trials in the ICU

A strong argument that waiving consent may be appropriate for some RCTs was put forward by Truog and coworkers [5]. They base their position on the frequently poor comprehension of the RCT process and of informed consent documents by patients or surrogates. A waiver of consent could be obtained from an institutional review board provided the treatments offered in the trial are available outside the trial without the need for consent, the study carries only minimal additional risk, genuine equipoise exists among the studied treatments, and no reasonable person should have a preference for one treatment over any other. In the letters published in response to this thoughtful paper, the risk of jeopardizing patient autonomy was the principal argument against the contention by Truog et al. [71]. Interestingly neither Truog et al. nor their detractors questioned the validity of the opinion that governed their debate, namely, that RCTs are useful under these special conditions. This is discussed below.

Solutions that require significant changes in the system

From the above it clearly appears that the debate on informed consent to research stems primarily from two axioms that can be questioned: care and research are two separate activities, and RCTs are superior to other forms of clinical research. Investigators should acknowledge that they cannot have their cake and eat it too: they cannot both enjoy the putative methodological advantage of an RCT and carry out their study without obtaining informed consent. Consent is inherent in the RCT process because it is needed to ensure compliance with basic ethical principles, most notably the principle of autonomy. Except in the rare cases of true emergencies (see above), there is no obvious ethical justification of waiving consent to RCTs.

Therefore if we want critical care to continue its amazing progress, we must rethink our research policies. First, the limited role (if any) of RCTs in this progress must be acknowledged. Second, the formal distinction between care and research must be reappraised. Third, current methodological dogma must be challenged.

Reappraising the formal distinction between care and research in the ICU

As stated by Miller and Rosenstein [3] in an article focusing mainly on RCTs, "Medical care is characterized by a convergence of the doctor's interests and the patient's interests.... By contrast, in clinical trials, the principal interests of the investigator and the participating patient may diverge." As mentioned above, the distinction between care and research was first made in the Belmont report [1] and should not be dismissed except in specific circumstances. Critical care may be one of these circumstances, given the consensus that "there is instead a spectrum that extends from established, evidence-based interventions through unproved therapeutic innovations to formal RCTs", as underlined by Truog and colleagues [71] in their response to the abundant correspondence generated by their publication [5]. It is important to bear in mind that most if not all of the debate on the therapeutic misconception concerns the distinction between care and RCTs [3, 4]. This distinction is obviously valid. However, clinical research can also have an integral role in clinical care [4], most notably when the interventions are not allocated at random. This offers an opportunity for reconciling the interests of the patients and those of the physicians, provided adequate methodological changes are implemented.

A plea for a methodological shift

Vandenbroucke and de Craen [20] wrote that "Sometimes we accept the evidence from the randomized trial and overturn a theory—however beautiful it was—but at other times we stick with the theory and dismiss the evidence." There is no inviolable scientific reason to prefer RCTs and their mandatory informed consent procedure to the well-being of patients and their proxies. There is, however, a moral obligation to improve the quality of critical care. Therefore alternative methodological approaches that protect both the welfare and the autonomy of patients should be given preference. These approaches should "find ways of accommodating clinical reality, not ignoring it" [26], and should require acknowledgement that RCTs can produce inconsistent results and can have limited external validity [26, 59]. Investigators will have to stop their obsessive quest for the so-called "absolute truth that can be given only by RCTs" and acknowledge the subjective element in the evaluation of science [20]. As underlined by Jerome Cornfield (inventor of both the odds ratio and logistic regression; cited in [20]), "good scientific practice... places the emphasis on reasonable scientific judgement and the accumulation of evidence and not on dogmatic insistence of the unique validity of a certain procedure." It is astonishing that physicians pressure institutional review boards (IRBs) to accept waivers of consent and zealously lobby for changes in regulations that they feel may "impede research" [11, 12] without questioning the validity of the diktats issued by a number of methodologists and journal editors. The real problem is not to obtain a waiver of consent to RCTs from patients or proxies: the consent that we need is that of methodologists, from whom we seek creative study designs, and of medical journal editors, from whom we ask for greater openness to contributions that are less highly ranked in the pyramid of evidence-based medicine [14].

Trials with prerandomization. This design was introduced by Zelen [72]. Patients are randomly preallocated to the conventional or new treatment before they are asked to consent to the study. In the patients allocated to the control arm no specific consent to research need be obtained. In contrast, informed consent is sought from the patients (or proxies) in the group allocated to the new treatment; when consent is refused, the patient receives the conventional treatment. This appealing design requires unblinded treatment administration, which is the case in many trials in ICU patients (most notably on procedures). It has been used in pediatric trials of extracorporeal membrane oxygenation [73, 74]. Prerandomization may increase patient inclusion rates. Studies have calculated the "price of autonomy," that is, the number of lives that may be lost if the inclusion rate is slower because prerandomization is not used, resulting in delayed implementation of a life-saving treatment [49, 75].

However, ethical objections to prerandomization [76] include denial of information, using people, denial of choice, and "overselling" of allocated treatments [77].

Observational studies. Well-conducted observational cohort and case-control studies can provide the same level of internal validity as RCTs [59, 78, 79]. They are particularly well suited to research in the ICU. Indeed, as mentioned above, blinding is neither necessary nor feasible for most therapeutic interventions in the ICU. In fact most of the major recent RCTs were unblinded [28, 36, 37, 80, 81, 82, 83]. Why not evaluate new therapeutic interventions sequentially under conditions of genuine equipoise? In such conditions, rather than a detailed explanation of the randomization process, "such an elegant, reliable, sophisticated concept to the research clinician, but so brutal and harsh from the patient's view point" [62], only consent to general care [84] and to the use of data obtained during usual patient care for research purposes [85] would need to be obtained. Renunciation of RCTs in favor of observational studies does not imply that physicians have a free hand on their patients. IRB approval and close monitoring of data quality and patient safety would still clearly be needed. In addition, cohort studies are probably the only option left for emergency research when legislation prohibits the waiving of consent, as may unfortunately become the case in the European Union within the next few years [11, 69]. Interestingly, this approach was used in a recent study of thrombolytic therapy after initially unsuccessful cardiopulmonary resuscitation [86]. The cohort design deserves to be considered before the alarm is sounded for the questionable reason that research in emergencies may stop if RCTs are no longer feasible [10, 12].

The case of industry-sponsored research

These are among the most dangerous studies, as recently shown by the results published for several new drugs in ICU patients [52]. Furthermore, by definition there is a risk of major conflicts of financial interest. It follows that patient protection should receive particularly careful attention, and that the studies must be completely free of potential methodological weaknesses and ethical flaws. Clearly such studies must be randomized (which is mandatory anyway for obtaining regulatory approval). In addition to a thorough review of the research protocol by a completely independent IRB, unblinded monitoring of adverse effects should be conducted, as recently suggested by Freeman and coworkers [52]. Finally, the informed consent document should provide detailed information and receive careful scrutiny by the IRB. For instance, a fair informed consent document on new therapies for sepsis should explain what physicians know, namely, that the pathophysiology of sepsis is incompletely understood, and that the animal models on which the clinical trial is based are not fully valid [51]. In addition, if another new treatment was associated with increased mortality rates in other studies [52], this fact should be disclosed. Finally, the amount of money received by the physicians or their institution per patient included should be indicated, as well as any financial interests linking the physicians to the drug company (e.g., shares owned or position as paid consultants), as suggested by organizations such as the Alliance for Human Research Protection (http://www.researchprotection.org/InformedConsent/InformedConsent.html, accessed 19 July 2004). Patient autonomy should not stop where potential financial profit begins.

Increased oversight of research

As pointed out by Luce [53], stronger research oversight may be as important as informed consent in protecting patient welfare. Since we contend that, provided investigators desist from performing RCTs, formal consent to research need not be sought and consent to care and to the use of data is the rule, it also holds that research oversight must be reinforced [58, 66, 65, 87]. Research projects that do not require specific informed consent should be examined thoroughly by IRBs, which should obtain the opinions of independent consultants if needed. The primary goal is not to make research easier for physicians but to increase the safety of patients and proxies. If greater ease of research occurs as a side effect, this will be welcome.

In conclusion, RCTs were born under a shroud of original sin consisting of financial, political, and academic pressure. This was summarized by Yoshioka [88] in a publication about the Medical Research Council trial on streptomycin: "The innovation of centrally controlled randomisation can be attributed to a combination of scientific logic and political and social pressures on medical bureaucracy." This sin may have remained unredeemed, as suggested by the extraordinary controversy about the ARDS Network study [60, 89]. Before deciding which clinical study design is best suited to critically ill patients, consideration should be given to several points:

- Many RCTs in critical care generated heated pro–con debate during medical conventions yet failed to improve patient care.
- Respect for patients and their families requires that investigators refrain from using a plethora of informed consent documents which constitute a perversion of ethical principles but rather wield this two-edged sword with discernment.
- Clinical trials should be conducted not to achieve methodological purity but to improve patient management.

– In clinical trials the best possible compromise should be sought between the ethical principle of beneficence to the patient and that of nonmaleficence to the proxy, who is asked to give consent while struggling with overwhelming distress.
– Clinical trials should be appraised according to the ethical principle of distributive justice: what cost for what result?
– Society is changing and may no longer be ready to accept what many persons may consider, rightly or wrongly, to be a manifestation of medical power.

The effects of the AIDS epidemic on patient mentalities and the growing influence of organizations such as AHRP should be pondered. Similarly, owing to widespread public concern about the adequacy of protection for human research subjects, litigation against investigators, IRBs, and academic institutions is becoming increasingly common [90]. Then, nolens volens, clinicians may have to forbear conducting RCTs for ethical, scientific, sociological, legal, and financial reasons. One solution may consist in giving preference to forms of clinical research that are tightly linked to care. Clinicians should work closely with innovative methodologists to find new designs that are acceptable to all. Clinicians serve patients. And methodologists serve clinicians, not the opposite.

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