Of Consents and CONSORTS: Reporting Ethics, Law, and Human Rights in RCTs Involving Monitored Overdose of Healthy Volunteers Pre and Post the “CONSORT” Guidelines

Thomas A. Faunce,1,2,* B.Med, L.L.B., Ph.D., and Nicholas A. Buckley,1 M.D., F.R.A.C.P.

1Faculty of Medicine and 2Faculty of Law, Australian National University, Canberra, Australia

ABSTRACT

Randomized controlled trials (RCTs) of therapeutic interventions in acute drug overdose present a significant challenge for ethical, legal, and human rights protections of research subjects, particularly when healthy volunteers are involved.

The CONSORT statement on the uniform reporting of clinical trials was published in 1996 with the overall aim of improving the reporting of RCTs, both individually and to facilitate their inclusion into systematic reviews. In CONSORT, reporting of ethical, legal, and human rights protections, including prior evaluation of the study by an ethics committee and provision of informed consent, was largely an implicit requirement.

Those drafting CONSORT may have assumed such protections and the rights of study subjects were secured by existing doctor–patient relationships. Alternatively, CONSORT may have been viewed as likely to indirectly enhance such protections, as a flow-on effect of improved RCT design and reporting. We wished to examine whether such assumptions were justified by examining the reporting of RCTs of simulated overdose in healthy volunteers.

We reviewed all reported RCTs involving activated charcoal in healthy human volunteers for three years before the CONSORT statement (1989, 1990, and 1991) and three years afterwards (1999, 2000, 2001). Presence of documentation of inclusion and exclusion criteria, stopping rules, protocol deviations, information sheets, consent documentation, ethical approvals, conflicts of interest, understanding, refusal, inducements and coercion were recorded.

We found a very poor level of reporting of some key ethical, legal, and human rights protections for healthy volunteers in toxicological RCTs. Reporting did not improve with the publication of CONSORT even in relation to requirements specifically included in the guidelines.

Key Words: RCTs; Volunteers; Overdose; CONSORT; Ethics.
INTRODUCTION

Ethics, Law, and Human Rights Protections Relevant to Toxicological RCTs

There are a number of difficulties with conducting research in poisoned patients and extrapolating animal results to human populations (1). Thus despite the risks, studies exposing healthy volunteers to therapeutic interventions during simulated drug overdose are likely to remain an important source of knowledge for clinical toxicological practice.

As these investigations involve no active treatment of disease, subjects involved are not necessarily covered by the implicit ethical, legal, and human rights protections of an existing doctor–patient relationship. The research protocol, consent form, and report are the only practical means of verifying attempts and success at implementation of the necessary protections.

Good trial design excludes high-risk patients, such as pregnant women, those on medications, or with significant illness (2). Similarly, stopping rules, calculation of the upper safe dose limit, protocol deviations, proof of voluntary entry (measures taken to avoid possible inducement, intimidation, or coercion), and adequate disclosure of material risk should all be part of the protections given to volunteer research subjects (3,4). A higher standard for disclosure may apply to informed consent for RCTs involving healthy volunteers (5).

Guidelines on informed consent issued by the Council for International Organisations of Medical Sciences (CIOMS), Article 7 of the International Covenant on Civil and Political Rights (ICCPR) and the Declaration of Helsinki (2000), support these protections. The latter provides in article 22:

“After ensuring that the subject has understood the information, the physician should then obtain the subject’s freely-given informed consent, preferably in writing” (emphasis added) (6).

Healthy volunteers may place reliance on the expertise and good intentions of nominated research ethics committees and, of course, the researching doctors involved, to protect them from harm (7–9). The difficulty here is that the deliberations and determinations of these committees are not currently transparent or apparently consistent in either process, content, or prior training of members. Consequently, explicit reporting of the number of proposed research subjects who refused informed consent may be one of the best indicators of how properly informed all subjects were and how conscientiously investigators ensured that they enrolled by free decision (10,11).

Informed consent and IRB approval are now widely recognized as an important part of any RCT protocol. Yet, a study of the reporting of such protections in major medical journals (NEJM, JAMA, Lancet, and BMJ) between 1993 and 1995 revealed that approximately 25% failed to mention (and of these 20% had failed to seek or request) confirmation of either (12). A further study in 1997 of 195 reports of clinical trials in specialist journals revealed that only nine reported the informed consent rate, with refusal varying between 0 and 84% (median 7%, mean 25%) (13).

The Consort Statement: Its Aims and Deficiencies

The CONSORT statement was created in 1996 to improve overall standards in the reporting of all RCTs (14). CONSORT arose from two independently published proposals to tighten the reporting of randomized trials published in 1994 (15,16). The statement comprised a checklist of 21 items pertaining to methods, results, and reporting; information necessary to evaluate the internal and external validity of an RCT. The CONSORT statement is available on the World Wide Web (www.consort-statement.org) and was last revised in 2001 (17). Since its publication in 1996, CONSORT has been supported by an increasing number of medical journals and has been endorsed by the International Committee of Medical Journal Editors (18). There has been a major improvement in the quality of reporting of RCTs in all journals, but greater improvements were seen in those that had explicitly adopted the guidelines (19).

Informed consent and other ethical, legal, and human rights protections were not mentioned specifically in CONSORT, though they appeared to be regarded as implicit in a number of different items. For example, CONSORT required the following items to be reported: the planned study population with inclusion/exclusion criteria, prospectively defined stopping rules, full details of the randomization process, full details of participant flow, and deviations from the planned study protocol.

We wished to systematically examine a recent, representative series of RCTs involving monitored drug overdose in healthy volunteers to determine whether the promulgation of CONSORT had improved reporting of ethical, legal, and human rights protections in RCTs where such matters are most pertinent (17).

METHODS

We looked at all trials reported as being randomized and involving healthy volunteers, activated
charcoal and monitored drug overdose in three years prior (1989, 1990, 1991) and three years after, initial publication of the CONSORT statement (1999, 2000, 2001). The earlier period was selected as clearly preceding the earliest discussions on CONSORT.

A Medline search was performed with the MeSH headings *Charcoal, limited to English, all adult and human. These were further restricted to randomized controlled trials and the years of publication 1989–1991 (group1) and 1999–2001 (group2). Resulting articles were then reviewed to determine if they were performed in “healthy volunteers” (not “patients”) and an oral “overdose” (greater than usual therapeutic dose) had been administered. It was decided to examine only one example from the same first author in each group.

Each trial was checked independently by the authors for the presence of key words or closely related concepts, relevant to aspects of the explicit CONSORT criteria most relevant to ethics and human rights protections. The selected explicit CONSORT aspects were Item 4 in “Methods,” “describe planned study population, together with inclusion/exclusion criteria.” We also looked at Item 8, “describe prospectively defined stopping rules,” and Item 19, “describe protocol deviations from the study as planned, together with the reasons.” These were then included in a brief list of key words, or related concepts signifying important ethical, legal, and human rights protections.

Simulated overdose studies also often involve volunteers from populations potentially vulnerable to financial or social inducements or coercion (traditionally medical or other university students or employees) (20). We looked for documentation in the RCT protocol that subjects were not in a dependent relationship with any of the investigators and were free to withdraw at any stage without prejudice to subsequent medical care or payment of the honorarium (4).

The final list became “inclusion/exclusion criteria,” “stopping rules,” “protocol deviations,” “information sheet” “informed consent,” “ethics committee or IRB,” “understanding/refusal,” “conflict of interest,” “inducement/coercion,” and “signed consent form.”

RESULTS

The results are set out in Table 1. RCTs are grouped in the two different time periods (1989–1991 and 1999–2001). They show it was common for published reports of these RCTs in both periods, to mention the explicit CONSORT requirement of inclusion and exclusion criteria, and the implicit requirements of IRB approval and informed consent. In neither period, however, was there mention of the explicit CONSORT requirement of prospectively defined stopping rules. There was no improvement in the inconsistent reporting of the explicit CONSORT requirement of protocol deviations.

In neither period was there any detailed reporting of other important ethical, legal, and human rights protections. No examined reports, in either period, mentioned whether subjects read an information sheet, had their understanding of its contents checked, were unambiguously permitted refusal without penalty, and whether inducement or coercion was considered. Similarly in neither period was there detailed reporting of whether the consent form was signed or whether the investigators had a potential conflict of interest.

In both periods, explicit reference to the relevant protections (apart from inclusion and exclusion criteria) was confined to paragraphs such as “The study was approved by the [relevant research ethics committee] and informed consent was obtained from each participant,” (21) or “The study protocol was approved by the [relevant research ethics committee and Medical Faculty] and signed informed consent was obtained from each volunteer. The volunteers received an honorarium for participation” (30). The latter provided the only explicit reference to any form of inducement in all the examined studies.

DISCUSSION

The preeminent ethical principle derived from the Helsinki Declaration is that in any medical research the well-being of the subject should always take precedence over the needs of science or the interests of society (34). This principle underpins the requirement in the Nuremberg Declaration and Article 7 of the ICCPR that no research be performed upon a human being without his or her “free” consent (16). Judicial decisions and legislation in most developed nations support these propositions (35).

We have found that these important ethical, legal, and human rights protections are not being reported in toxicology RCTs where their existence and application are particularly relevant. This problem, is by no means confined to clinical toxicology studies (36), and the publication of the CONSORT guidelines appears not to have significantly improved matters. This is of particular concern given reports of recent deaths of health volunteers in clinical research much less presumptively dangerous than that discussed here.
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>McNamara et al (1989) (21)</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Eisen et al (1991) (22)</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Keller et al (1990) (23)</td>
<td>Yes</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Yeates and Thomas (1999) (28)</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Implied</td>
</tr>
<tr>
<td>Green et al (2001) (30)</td>
<td>Yes</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Yes/ Honorarium</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Unless otherwise stated ("yes" or "implied") no reporting of the relevant item occurred. IRB: Institutional Review Board, Research Ethics Committee.
Reporting Ethics, Law, and Human Rights in RCTs

The consequences of a breakdown in ethical, legal, and human rights protections in this area can be severe both for the healthy volunteers, the researchers, and their institution. In March 1999 a healthy volunteer at the University of Rochester Medical Center died after receiving 28 instead of the recommended 10 brushings with topical lignocaine (to facilitate research bronchoscopy). This overdose lead to a back-extrapolated plasma concentration of 36 mg/L (155 μmol/L) [maximum safe concentration of 5–6 mg/L (22–26 μmol/L)]. The research protocol had no upper dose limit (4).

On June 2, 2001, a healthy volunteer due to receive a $365 honorarium, died from diffuse alveolar damage after participating in a study at the Johns Hopkins Asthma and Allergy Centre involving inhalation of hexamethonium, a drug no longer in clinical use. The Federal Office for Human Research Protections found that the institution’s research ethics committee (or institutional review board, IRB) had been attempting ongoing review of up to 800 new proposals with biweekly meetings, had kept no minutes for 18 of its last 21 meetings, and failed to review most protocols undergoing initial review. It had also not checked a consent form that misleadingly gave more assurance of safety than data warranted, or attempted to inhibit a culture of “possible coercion” of employees and students to volunteer for RCTs. Federal research funding was temporarily suspended (37).

In the United States, such problems have led the Office of the Inspector General of the Department of Health and Human Services to conclude that IRBs in that country are often forced to review “too much, too quickly, with too little expertise” (38).

The death of any healthy volunteer will have major implications for all research in the institution involved. If this occurs in a clinical toxicology study it will have a particularly dampening effect upon further research in this area. It may, for example, lead to independent external review of the extent to which the protections discussed here are being implemented and reported. Proven failure to comply may result in funding restrictions, mandatory restructuring of relevant policies and procedures, and delays in research approval.

For these reasons the publication policy of major journals should send the signal that compliance with and detailed reporting of ethical, legal, and human rights protections is important. This is particularly true in toxicological research involving healthy volunteers. The intent (but not the implementation) of Article 27 of the *Helsinki Declaration* is quite clear:

“Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication” [emphasis added].

Others have recently drawn attention to the need for more detailed reporting of ethical issues in publications of medical research (39). Their main argument is that research may still be ethical in purpose while involving morally controversial methodology. Current practice in scientific publishing may reflect a false dichotomy between “ethical” and “nonethical” research that truncates any discussion of ethical issues. Authors should rather be given the opportunity to justify their choice of study design in ethical terms and to outline the steps they undertook to maximize protections for the research subjects.

We make no claim that the trials discussed here, or for that matter any other published volunteer studies in clinical toxicology, have been conducted in contravention of the *Declaration of Helsinki* or other ethical and human rights protections. Our point is to make the protections discussed here truly transparent and capable of independent analysis and verification. This is analogous to the expectation that an RCT published in accord with the CONSORT guidelines will have sufficient details on the trial design and outcome data to allow most bias to be suspected or detected.

An ethically and human rights enriched modification of CONSORT could be published and applied by journal editors to healthy volunteer studies involving deliberate, monitored overdose. If publication space is a concern more detailed discussion of these issues could be placed on the journal’s web site.

The on-line (or print) publication of information sheets, consent processes, ethical approval, and outcomes may have significant advantages to those who subsequently wish to perform clinical toxicology research in healthy volunteers. Such publications could serve as reference points to which local IRBs could be directed—establishing and developing ethical, legal, and human rights “norms” for research in this field.

REFERENCES