

Are distinctive ethical principles required for cluster randomised controlled trials?

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Summary

Cluster randomised trials are increasingly used in research into health care and health services. Ethics of individual patient randomised trials have been elucidated in a number of different codes, but less attention has been given to the ethical issues raised by cluster randomised trials. We assess the challenges raised by cluster randomised controlled trials by considering three questions:

What are the essential elements of ethical medical research, particularly experiments on people?

What are the features which distinguish cluster randomised controlled trials from ordinary RCTs?

Do the distinctive features of cluster randomised trials entail new ethical principles, or careful application of existing principles?

We conclude that cluster randomised controlled trials raise new issues on the nature and practice of informed consent, because of the levels at which consent can be sought, and for which it can be sought. In addition, careful consideration of the principles relating to the quality of the scientific design and analysis, balance of risk and benefit, liberty to leave a trial, early stopping of a trial and the power to exclude people from potential benefits is required.

1 Introduction

The need for regulation of the conduct of professionals who carry out experiments on human subjects was recognised a century ago, in Germany [1]. The inhumane experiments carried out by doctors under the Nazi government clearly contravened the existing laws. After the war crimes trials in Nuremberg, a code of conduct was drawn up, and there are now many international codes governing research on people [2, 3, 4, 5]. These codes generally assume that experiments on people involve them as individuals, not as part of a larger social unit.

Cluster randomized designs (CRD)¹, in which intact social units are allocated different interventions, are increasingly used in health care and health services research. It is timely to consider whether any particular ethical issues are raised by this form of study, which are not present in clinical trials in which individual patients are screened for eligibility and offered entry to the trial.

We will summarise the principles stated in the Nuremberg code [2] and the Declaration of Helsinki [4], with particular emphasis on the Nuremberg Code, which is simply expressed, and was devised by lawyers, who should be less influenced by personal considerations of health care (this can, of course, cut both ways.) After describing the distinctive features of cluster randomised trials, the ethical principles particular to cluster randomised trials will be discussed.

Although informed consent is essential to ethical research[6], it is not the only principle which must be considered with regard to cluster randomized trials. The scientific validity of the design and analysis of a study, the freedom to leave a trial, and the early stopping of a trial will also be affected by the change of the unit of randomization.

¹The abbreviation CRD (cluster randomization designs) is used to avoid confusion with the abbreviation RCT for randomized controlled trial

It is helpful to consider whether suggested modifications to principles could be interpreted such that some of the Nazi experiments which gave rise to the Nuremberg code would be permissible. Although there is general agreement that the various Nazi experiments were unethical, specifying exactly what was wrong is not simple [7]. The experiments were conducted against a background belief that eugenics was a valuable science, a belief which was widespread in the Western world, and is not without present day adherents. Extreme examples are used in order to challenge and clarify our pre-conceptions. The Nuremberg code cannot be completely adhered to in all trials, but any divergence from it requires very careful argument.

2 Control of human experiments: The Nuremberg code

Ten standards were laid down by the war crimes tribunal at Nuremberg to which physicians (or others) must conform if an experiment on human subjects is to be permissible[2]. A brief précis of the standards is given here, to inform the subsequent discussion. *Editor: should the complete code be given?*

1. "The voluntary consent of the human subject is absolutely essential. ...The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity."
2. "The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods ..."
3. Previous knowledge must be used in designing the experiment, and justify the need for it.
4. "The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury."
5. "No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur ..."
6. "The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment."
7. "Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability or death. "
8. "The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment."
9. "During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible."
10. "During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject."

The Helsinki Code gives similar principles, but in a different order[4]. Informed consent is not given the prime position, and the possibility of situations in which a "physician considers it essential not to obtain informed consent" (sic) is presumed. Conformity to "generally accepted scientific principles" is required, but physicians are stated to be free to introduce "new diagnostic and therapeutic measure" outwith a controlled study, on the basis of individual judgement. Physicians "can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient."

In an article which gives the historical and ethical background to human experiments, WHO/CIOMS guidelines

are given [8]. With regard to “Community-based research”, these guidelines state:

“ 16. Where research is undertaken on a community basis - for example by experimental treatment of water supplies, by health services research or by large-scale trials of new insecticides, of new prophylactic or immunizing agents, and of nutritional adjuvants or substitutes - individual consent on a person-to-person basis may not be feasible and the ultimate decision to undertake the research will rest with the responsible public health authority.

17. Nevertheless, all possible means should be used to inform the community concerned of the aims of the research, the advantages expected from it and any possible hazards or inconveniences. If feasible, dissenting individuals should have the option of withholding their participation. Whatever the circumstances, the ethical considerations and safeguards applied to research on individuals must be translated, in every possible respect, in the community context.” [8, p 1447]

3 Cluster-randomisation trials

Cluster-randomisation designs are experiments in which intact social units are randomly allocated to one of two or more intervention or treatment strategies [9]. The fact that the unit of randomisation includes several patients or participants has implications for both consent and the science of CRDs.

I elaborate this basic description of CRDs: reasons for using CRDs are given, important structural features are listed, and then examples of different trails are given.

3.1 Reasons for using CRDs

There are several reasons, some scientific and some practical, which can be given to justify the use of CRDs.

Scientific reasons

Cluster action of an intervention A drug might act at both individual and community level. For example, vaccines work by reducing the likelihood of becoming infected, reducing the severity of the infection and reducing the transmission of the disease. Drugs for treatment of river blindness can also reduce the rate of parasite transmission to the black fly vector[10]. Thus trials of the impact of vaccines and some drug treatments cannot be evaluated in isolated individuals.

Cluster level intervention Some interventions are aimed at professionals, or teams of professionals. Their care of their patients can only be evaluated at a cluster level.

Treatment cluster contamination If an intervention aims to change social behaviour, or transmit knowledge, avoiding contamination of the control or alternative intervention clusters might require separation in space or time.

Enhance subject compliance Interventions in a general practice, school or workplace might be enhanced by discussions between subjects, informal as well as formal. This might be integral to the intervention.

Logistical and political constraints

Administrative convenience Using clusters allows personnel to be concentrated in a few locations, rather than having to travel widely. Professionals might only co-operate if they do not have to change practice for each patient. Access to patients might only be available through professionals, so that individual randomisation would require large numbers of individual professionals to be contacted and requested to pass on trial information.

Political It might be necessary to obtain permission from national and local governments or community leaders before proceeding to contact individuals.

Access to routine data In order to obtain information, relevant administrative or archiving authorities, such as general practices or hospital trusts, might have to be approached.

Cluster randomisation is less statistically efficient than assigning individuals at random, unless there is no correlation within clusters. The analysis of results must allow for the structure of the randomisation. Clusters tend to have various characteristics in common, and therefore show some intra-cluster correlation. Even a small intra-cluster correlation can have important implications for sample size, if the clusters are large. Some improvement in efficiency can be gained by using matched or stratified designs. In general, it is more important to have sufficient clusters than large clusters. *Cross-reference within this issue.*

3.2 Important structural features of CRDs

There are a wide variety of CRDs, and many different levels and ways in which people are involved in them. The essential question or hypothesis addressed by the trial will have implications for the trial design. I list features which are relevant to ethical considerations. A full cross-classification is not attempted here.

Units of randomisation or allocation The unit of randomisation might be entire social units directly (households or whole villages), or indirectly, such as people within a general practice who are, or will be, diagnosed as having a disease which is the focus of an intervention at practitioner or practice level.

Experimental units The people to whom the intervention is primarily applied, are not necessarily the same as the units of randomisation or observation. The direct recipient of the intervention might be the professional carer, or the patient.

Units of observation The outcomes of interest might be measured on those directly receiving the intervention, or on people intended to benefit indirectly: practitioners' knowledge might be assessed, or the changes in their patients' health. The measurements chosen to evaluate the interventions might be available from routine records. If the observational units are not the experimental units, then they might not be contacted directly, as access to patient notes might be sufficient. We therefore need to distinguish between consent to an intervention, and consent to data collection. This distinction is often not explicit in RCTs.

Gate-keepers Gate-keepers are people in either political or administrative positions who are able to give consent for those within a cluster to be randomised. They will not necessarily receive the intervention themselves.

Available alternatives The alternative to the experimental intervention might be standard care, or a placebo. The concept of 'placebo' within health service research might repay further study. As with RCTs, the experimental interventions might not be available outwith the trial.

Ease of withdrawing from a trial In some instances, a participant can easily withdraw. In other circumstances, this is difficult, or impossible - if an insecticide is sprayed throughout a village.

3.3 Examples of CRDs

1. Two instruments for taking cervical smears were evaluated with randomisation of general practices and family planning clinics willing to participate[11]. One instrument was used within a practice, for logistical reasons. Each woman was asked for consent to enter, and could withdraw and, in principle, have been given the alternative intervention.
2. Women in Nepal of child-bearing age were recruited through administrative districts which were randomly assigned to receive vitamin A, β carotene or placebo supplements [12]. Written consent was obtained from sub-district leaders, and verbal consent from the individual women. Here, gate-keepers might also be subjects. Refusal of the intervention is possible. It is not clear whether women who declined to enter the trial were able to obtain vitamin A or β carotene.

3. A drugs education programme can involve randomising schools to receive different educational packages. The local authorities, head teachers and teachers would be involved in the decision to include a school. The outcome might be children’s knowledge. It is fairly easy for a child to be withdrawn from classes, but information can be passed between classmates. The gate-keepers would not be subjects.
4. Households could randomly assigned to receive a domestic water filter or to continue using ordinary rain water collected from the roof. Each household can be asked to consent. The gate-keepers would be subjects.
5. Fluoridation of water supplies is implemented for communities. It is difficult to offer each person an alternative water supply, although some people could buy bottled water. The opportunity to withdraw is limited.
6. General practice teams were assigned to receive additional training in care of people with newly diagnosed diabetes [13]. Both physiological and quality of life measures were used to evaluate the intervention. It is difficult to offer patients the alternative intervention, or for them to withdraw, as this implies offering them a change of general practice.

Although some of those who have contributed to the current debate about revising the Declaration of Helsinki believe that different standards should be applied to developing countries, I do not [14], and the principles discussed in this article are intended to be applied to all people, not merely some races. The final example is in the field of implementation research. Implementation research raises further issues, which will be addressed in future research.

4 New issues regarding informed consent

The different levels of randomisation and intervention mean that there are potentially various types of consent and levels at which it can be sought. Some aspects of these issues also arise in RCTs.

4.1 Levels at which consent might be sought

We usually think of consent as operating at the level of the individual person, but further reflection shows that in RCTs consent is sought from at least two levels: ethics committees and the patients. With CRDs, there are further levels to consider.

Ethics committees In the Helsinki code, when a “physician considers it essential not to obtain informed consent”, she is required to submit her reasons to an external body. Ethics committees or institutional review boards are the obvious bodies to take responsibility for assessing the validity of the reasons given for not seeking consent. The complexity of design and analysis of CRDs suggest that statistical expertise will be required by ethics committees [15].

Ethics committees are in some sense far removed from the interventions, in that the committee members are unlikely to be experimental or observational units in trials they consider.

Grant awarding bodies Bodies which initiate research have a duty, under the Nuremberg code, to assess the quality of consent obtained from human subjects.

Community consent If communities are chosen as clusters, debates about community consent might be particularly relevant [6]. For RCTs, community consent would be consent for individuals to be approached [16]; for CRDs, community consent might be consent on behalf of individuals. How a community is defined, and how its representatives are chosen, takes the debate into political philosophy. Detailed integration of ethics of community consent with aspects of political and social philosophy is left for future work.

Community leaders are quite likely to be directly affected by the decisions they make. However, a Nigerian study indicates that the leaders’ views, which are cheaper and easier to obtain, cannot be relied on as proxies for the opinions of heads of households [10].

Professional consent Health professionals will often have legal requirements which they have to satisfy before allowing access to patients on their lists.

Household consent Although it has been suggested that in some cultures heads of household might give or withhold consent for adults in their household, there is no firm evidence of this, so it has the status of a prejudice [6].

Experimental subject The Nuremberg code requires this level.

The Nuremberg code emphasises that individual researchers cannot delegate their responsibility for ensuring that consent is voluntary.

4.2 Consent to what?

The information provided when consent is sought might be more complicated than that required for RCTs. Consent might be sought, or not sought, at some of the various levels, for

1. the use of routinely held data,
2. collection of additional data, with or without the use of invasive procedures, or
3. the offer or administration of an intervention.

The ideal is to have consent sought at all levels for both the intervention and for additional data collection. One of the practical issues that has to be faced by those doing CRDs is the best way to explain a trial to people who are allocated to a control arm, and who will receive routine care. If a patient is in a practice which has been randomised, one might have to explain that what is sought is not consent to an intervention but consent to data collection.

In RCTs, people who decline to enter a trial cannot necessarily obtain their treatment of choice, so the fact that a person in a cluster who refuses the allocated intervention cannot always get their preferred alternative is not a problem unique to CRDs. Information can be provided even if the patient does not have a feasible alternative intervention and cannot withdraw. The value of courteously providing information should not be underestimated, although it is possible that the result might be either an increase in goodwill, or increased patient concern. Failure to provide this information risks psychological harm, as subsequent discovery of inclusion in an experiment might result in a sense of violation [16, 17].

4.3 Feasibility of informed consent

The necessity and feasibility of obtaining voluntary individual informed consent (VIIC) from all those who are subject to the treatment or intervention depends on the nature of the study and the intervention. A distinction between experimental and epidemiological research is important in considering the necessity for obtaining VIIC. In epidemiological research in the United Kingdom, data is generally collected from work records and patient notes without explicit individual consent. This is generally accepted practice (endorsed by MRC guidelines). In order to be exempt from a requirement for VIIC, a study would have to have an intervention at the level of a practice or practitioner, and not be intended to affect patient care.

A common distinction between experimental and epidemiological research is the presence of an intervention which the researchers manipulate. It can be hard to determine where research begins in areas where there is more or less continuous innovation [16]. The difference in standards of consent for routine and experimental care which has been discussed for RCTs [18] is more difficult in the context of health services research. Detailed consideration of this is left for future research.

Serious consideration must be given to the feasibility of informed consent. Helsinki II recognises that some interventions would be vitiated by requesting informed consent. In this case, the researchers are expected to let an

independent committee assess the validity of the reasons for not requesting consent. This particular case is no different in RCTs and CRDs: safeguards are crucial in both.

The second major discussion on feasibility relates to administrative and scientific considerations. The latter concerns bias which arise due to differential consent, and is discussed in the section below on timing of consent.

The WHO/CIOMS guidelines accept the possibility that individual consent is not feasible. The decision to undertake the research is to be made by a ‘public health authority’, with attention given to providing the community with information on the research [8]. This authority must therefore take responsibility for the consequences of the research, although the people who are such authorities might not themselves be directly exposed to the interventions. However, it is not obvious that there will be only one authority which can, or should, take such decisions and responsibility. One of the examples given in Helsinki II is of ‘large-scale trials of new insecticides’. If the insecticide were to be used against malaria, the decision to allow a village community to be included could involve decisions by national and regional government, as well as individual villages. Clearly, there is a close connection between the decisions made as a ‘responsible public health authority’ and a political authority, democratic or otherwise. If the boundaries of jurisdiction of public health authorities, and political authorities are not the same, which authority should take priority in making the decision to allow the trial to go ahead? And where contamination is possible, even with larger clusters, the number of authorities who can reasonably expect to be consulted increases. The role of public health authorities or gate-keepers in CRDs should be to inform those planning the trial of local conditions which require special consideration, and to inform the members of the cluster about the trial.

The Nuremberg code was drawn up as a result of the failure of political authorities to protect all groups of citizens. Effectively, informed consent was given by the state for the use of Jewish people, mentally ill people and other groups as experimental subjects, using utilitarian and eugenic arguments. Mere feasibility is not a strong reason to fail to request individual consent. The fact that subjects might not be able to avoid the treatment, although they do not consent to it, or might not otherwise have access to treatment, is a reason not to impose the treatment, not a reason to evade individual voluntary informed consent.

4.4 Consent and the nature of clusters

The suggested classification of CRDs into ‘individual-cluster’ trials, where the intervention is targeted at individuals, and ‘cluster-cluster’ trials, where the whole cluster is targeted, provides a starting point for considering informed consent in CRDs [19]. Both utilitarian ethics, and ethics concerned with people’s freedom to make decisions within society, under the law (Kantian ethics) are mentioned. Edwards et al assert that individual consent can only be sought in ‘individual-cluster’ trials. In ‘cluster-cluster’ trials, they claim there is a ‘guardian’, who has power to deliver the cluster, and “the role of the guardian is key to the ethical conduct of cluster trials”. Guardians are assumed by the authors to be advocates but they are not necessarily so. Hospital chief executives or head teachers might protect those under their care from harm, but this role is not the same as seeking to present a case for alternative treatment or no intervention. Perhaps one should argue that once a guardian is asked to give consent to a CRD, they ought to take on the role of advocate. Edwards et al expect their guardians to sign a consent form which states their duties: but if a guardian is not willing to accept the role of advocate, to whom should responsibility for the decision to enter the cluster be passed? It is not reasonable to determine entry to a trial by the willingness of people to change roles, though the fact that responsibility cannot be delegated must be borne in mind.

The authors suggest that guardians have to use utilitarian ethics when enrolling other people, and only volunteer their clusters if they think it is in their best interests. An alternative argument is possible. The opinion polls suggested by Edwards et al would not necessarily be utilitarian, but could address matters of belief and principle. A guardian could still regulate her behaviour autonomously by considering the arguments for the trial, and beliefs and principles concerning such matters as the nature of person-hood and whether people should be treated as means, or only as ends. She could devise means of informing people, or require that individuals be informed. Presumably those who enrolled concentration camp inmates could have done so on the basis of utilitarian ethics. Utilitarian ethics were the basis of the Tuskegee syphilis study.

Edwards et al (1999) claim that in CRDs, informed consent “cannot be obtained individually because one person’s choice will impinge on another’s”. This is false: there are CRDs in which individuals can be asked individually for

their consent. In the trial of Vitamin A or β -Carotene on pregnancy-related mortality, women were recruited after giving consent, and most health education interventions easily allow for individual consent. That ‘one person’s choice will impinge on another’s’ is neither unique to CRDs, nor does it render autonomous consent, that is, consent within the society and laws in which a person lives, impossible. When individual patients are randomised, because there will be a target number to be enrolled, the decisions of those given a choice of entry early in the trial will affect whether subsequent patients are offered that choice. Many decisions affect other people, and the allowing for those potential affects partly constitutes an informed, voluntary decision.

4.5 Refining categories of consent

Although the distinction between ‘individual-cluster’ and ‘cluster-cluster’ is useful in thinking about whether VIIC should be sought, the various dimensions of CRDs examined in section 3 show that further distinctions are needed. The unit of randomisation might include a well-defined, already identified cluster, but in some situations, the gate-keeper will offer consent for an unspecified group of subjects.

If the experimental units are not the observational units, then seeking consent from the experimental units might be feasible, and therefore mandatory. Obtaining consent from the observational units might be difficult, and arguably not essential. If there are no additional procedures, basically one is working within the rules which apply to the use of routine data. If there are questionnaires, or invasive procedures, it is possible to ask for consent to the procedures as part of ‘routine’ care, without mentioning the CRD. However, there is no good reason not to get VIIC, even if no alternative intervention is possible. As with requesting consent in RCTs, there is an expenditure of time, and possible differential acceptance rates. In some cases, experimental units, i.e. professional, might have a duty to enrol as part of their continuing professional development.

Intuitively, the consent of a gate-keeper who will also be a subject is more convincing than that of one who will not. One cannot be paternalistic to oneself. The common prohibition against enrolling prisoners or students as subjects indicates consent about decisions made by people in positions of authority which commit those over whom they have power to trial participation.

If there are multiple gate-keepers, one might have to respect consent from one person or body being vetoed by an individual within a consenting practice or by another body. This occurs with RCTs, as individual consultants can choose not to enrol eligible patients.

4.6 Power to exclude patients: access to benefits

One of the concerns of the Nuremberg code [2, point 7] is distributive justice: that risks and benefits should be fairly distributed. For CRDs, and for RCTs “... unjustifiable exclusions, and unjust and irrational uses of resources” [20] are matter for ethical criticism. That people who are in trials fare better on average than those who are not is fairly certain [21], although it is not clear whether this is mainly due to selection of participants or benefits arising from additional care given.

The power to exclude patients is not new in CRDs. That doctors do act as gate-keepers for individually randomised trials, by deciding offer entry to any of their patients, or offering entry to only some of the eligible patients, is known [22, 6]. The habitual exclusion of women from many trials in order to protect a possible fetus is an instance where women are denied the opportunity of participating in trials, and thus denied an opportunity for altruism, as well as possible benefit [16]. In CRDs, the formal right to consent to access to patients is coded differently, at least in some cases: a doctor or health team might be the focus of interest, rather than the patients. In CRDs, the authorities might have more power to exclude people from the benefits of trial participants.

Whether consent by general practitioners to some interventions which are aimed at improving patient care might be a professional duty is an issue which we leave to future research.

Of course, we cannot regulate all the opportunities and obstacles which arise in life. The possibility of enhanced

health care being available to those people who enter RCTs or CRDs is just one instance of this [16, 20]. Access to a trial might depend on the mis-fortune of having a medical condition which is a current focus of interest.

4.7 Timing of request for consent

Consent should be obtained before any intervention, but it is not ethically essential that it is obtained before decision as to what intervention would be offered if the person were to agree to enter the trial. The primary reason for obtaining consent before randomisation is a scientific one: it reduces the possible bias arising from different patterns of consent in the various treatment arms. One seeks consent to be in an experiment, not simply consent to a particular treatment.

Scientific and logistical constraints associated with CRDs imply that consent cannot necessarily be requested before an intervention is assigned to a person. If one regards trial entry and treatment assignment as equivalent, one creates an ethical problem because one regards people as having entered a trial, without consent, as soon as the cluster to which they belong is assigned an intervention. The assumption that trial entry and treatment assignment are equivalent is implicit in the claim that in cluster-cluster trials the trial entry and intervention form a single package, but do not in individual-cluster trials [19]: “In the case of cluster-cluster trials, therefore, a guardian must consent to or decline both trial entry and the intervention as a single package.”

In some cases it is logically impossible to obtain consent prior to randomising clusters, e.g. if an intervention is aimed at newly diagnosed patients, these people will not yet be identified. In the diabetes study, a person who does not have the disease when her practice is assigned, is nevertheless assigned to one intervention. However, there are circumstances in which one can get prior informed consent in ‘cluster-cluster’ CRDs: if the intervention is aimed at a household or village, for example, one can get consent from households before randomisation, even if intervention is targeted at the whole cluster (e.g. water filtration or diet modification). Another instance in which trial entry and intervention assignment can be distinguished is a vaccine trial. A person could refuse the vaccination, after their community had been assigned this intervention, which operates at both community and individual level.

Timing of consent has been discussed in connection with Zelen randomized consent designs. In this design [23], only those randomized to the experimental intervention are asked for consent, with a view to avoiding distress which might be associated with the request for consent. The real failure of the design is not in the timing of consent, but that a group of patients are enrolled into a trial without any consent. Some parents whose infants had been enrolled in a RCT expressed objections to the Zelen design, particularly those who would not have been asked for consent [17]. This suggests that some people whose care is affected by an experimental intervention would expect to be informed of this.

4.8 Popular uninformed consent

As some patients describe being asked for consent as cruel and unnecessary, or even unethical [24, 25], alternatives should be given serious consideration, and this might be thought to support the use of gate-keeper consent in CRDs. In the context of RCTs, the none of the alternatives are very satisfactory, because of inadequate patient protection, free-riding, unreasonable avoidance of decision-making and (self-)exclusion from optimal treatment [26]. It is, of course, possible that poor information, increased decision-making by doctors, and suboptimal treatment really are what patients or their advocates want. Cluster randomisation might reduce the distress arising from seeing one-selves as an individual guinea-pigs. However, having others enrol one in a CRD would run into most of the problems which arise in uninformed consent in RCTs.

5 Scientific validity and ethics of trial conduct

Six further principles in the Nuremberg code, which are concerned about with research methods, will be addressed in this section.

5.1 Sample size and statistical analysis

It is very likely that only those protocols which make adequate provision for professional statistical input are scientifically sound, and hence ethical in the light of Nuremberg 2, 3, 6 & 8. In terms of sample size, the effective size of a CRD is smaller than the total number of individuals studied, because of the similarity of people within clusters. Some investigators fail to realise that they are using a cluster design. For example, if two talking therapies are compared, two therapists might provide the treatment to a hundred patients. The effect sample size might be very small, of the order of two, because the personal nature of the treatment results in very high correlation of the response to treatment by a particular therapists.

Only about a quarter of CRDs considered in various reviews accounted for between-cluster variation when estimating the power of trials. Small trials are not necessarily unethical, provided the aim of the trial is consistent with its size. Thus large treatment effects can be excluded using small trials, and pilot studies are sometimes small. However, given such aims, the need to consider the appropriate size of the trial remains [15]. A hope that there will be other small trials which will be combined subsequently in an imaginary meta-analysis [27], is even less well-founded for CRDs than RCTs. The frequent use of complex interventions and collection multiple outcome measures in CRDs leaves open the possibility of selective reporting, with very serious consequences for meta-analyses [28]. Understanding of effect modifiers at individual and aggregate levels is often limited.

The need for appropriate methods of analysis is relevant both to the design and the analysis of the results, i.e. in assessing previous knowledge and in drawing inferences from the particular CRD. About half of reported CRDs reviewed allow for the clustering in the analysis. Thus any summary of previous knowledge (Nuremberg 2) might be affected by previous errors of analysis. The funding of a new CRD obviously must include provision for specialist skills to ensure correct analyses of past and current data. There might be confounding between provision of consent and the nature of clusters: a general practice which has an administrative system which can easily deliver letters seeking individual consent to patients might differ in many relevant aspects from those where individual consent is deemed not to be feasible. If a health team is allowed to exclude patients for unspecified reasons (e.g. terminal illness or cognitive impairment), then at least the rate of exclusions should be recorded and analysed. Methods are available to investigate informative missing data [29], but have implications who are defined to be “scientifically qualified persons” (Nuremberg 8). A particular challenge might be differential consent to standard and experimental treatments if consent has been sought after the clusters have been randomised.

In deciding the balance of risks taken against the importance of the problem to be solved (Nuremberg 6), thorough analysis of the risks and benefits is no less necessary than for RCTs. There is a temptation to think that preventive or educational measures carry no risks, and the new methods are better. However, any screening method will have false positives and negatives, which carry their own costs to people and to the providers of health care. It is easy to confuse ‘prevention’ with ‘hopes of prevention’ [30]. The belief that health education is important is a belief, and it is only one belief in the midst of many views of what constitutes value in human life [31, 30]. Some attempt to consider, and perhaps quantify the risks of any intervention should be made. Resource use is a further consideration, which again requires social and political categories of thought.

5.2 Liberty to leave a cluster randomised trial

In the case where a professional is the primary experimental subject, if she chooses to leave a trial early, she will effectively remove all her patients also (Nuremberg 9). If these patients do not wish to be withdrawn, they might be able to seek a transfer to another professional, although this will often be unrealistic. In some circumstances, such as talking therapies, where an essential part of the therapy is the interaction with the therapist as a person, it would not be possible for the patient to remain in the trial.

The opposite might happen: a practitioner might wish to remain in a trial, say of a method of delivery of care, and the patient might wish to withdraw from that care. Alternatively, an individual patient might wish to change their doctor in order to withdraw from the trial. Is it acceptable for this option of withdrawing to be withheld?

When the intervention is environmental, such as water filtration or treatment with fluoride, or spraying of insecticides, it might be difficult or impossible for the experimental subjects to withdraw, even if adverse events associated

with the intervention were reported.

5.3 Early stopping

Decisions about early stopping are dependent on planned and unplanned interim analyses, in CRDs as in RCTs (Nuremberg 10). The basic issues raised for (implicitly) RCTs include the decision as to what constitutes sufficient evidence, and the choice between evidence sufficient to change clinical practice and that sufficient to convince the research team [32]. The decisions might well be more complicated in CRDs, as there might be a need to accrue sufficient numbers in each cluster, and the point at which there is convincing evidence of benefit or harm might be very difficult to discern. Although there might be evidence to suggest that there are enough people with a particular condition within a cluster, it might take time for them to be identified. If a few clusters rapidly identify many subjects, and accrual is much slower in other clusters, the intra-cluster correlation will substantially affect the rate of accrual of information. Disadvantages associated with early stopping of a RCT, such as lack of credibility and realism, imprecision and bias [32] will be accentuated.

Again, this might be complicated if one is training professionals: if the training is rapidly shown to be beneficial, should one continue to accrue information while introducing training to other professionals. The time it takes to assess the intervention will depend on the choice of outcome measure: changes in a professional's knowledge can be assessed fairly quickly, but changes in practice which induce changes in health of patients could take years to become evident.

6 Discussion

There are new requirements for ethical conduct of CRDs. In contrast to RCTs [20], there are new issues with regard to informed consent for CRDs.

We have clarified the levels and nature of consent which require attention. Informed consent has to be considered and sought at several levels, and at no level can responsibility be delegated with impunity. It is not sufficient to obtain consent from only one level.

There is evidence that the scientific conduct of CRDs is not ethically adequate, and that matters of distributional justice, with political and social aspects, must be addressed. We have not addressed trials of educational methods or other work within the social sciences, but inter-disciplinary discussion will doubtless be valuable. Additional challenges are posed by concerns of access to resources, freedom to leave trials, and monitoring for early stopping of trials.

We believe that there remains more work to be done in clarifying and resolving ethical issues in cluster randomised trials, particularly with respect to intervention research.

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References

- [1] J Vollmann and R Winau. Informed consent in human experimentation before the Nuremberg code. *Brit. Med. J.*, 313:1445–1450, 1996.
- [2] The Nuremberg Code. (1947). *Brit. Med. J.*, 313:1449, 1996.
- [3] Council of the International Organisation of Medical Sciences. *International Guidelines for Biomedical Research Involving Human Subjects*. 1993. esp. Guidelines 1-3.

- [4] World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. 1964, 2000. <http://www.wma.net/>.
- [5] M Brazier. *Medicine, Patients and the Law*. Penguin, Harmondsworth, 2 edition, 1992.
- [6] R E Ashcroft, D W Chadwick, S R L Clark, R H T Edwards, L Frith, and J L Hutton. Implication of socio-cultural contexts for the ethics of clinical trials. *Health Technology Assessment*, 1(9):iv+65, 1997.
- [7] M Biagioli. Science, modernity and the “Final Solution”. In S Friedlander, editor, *Probing the Limit of Representation: Nazism and the “Final Solution”*, pages 185–205, 371–377, Cambridge, Mass., 1992. Harvard University Press.
- [8] N Howard-Jones. Human experimentation in historical and ethical perspectives. *Social Science and Medicine*, 16:1429–1448, 1981.
- [9] S B Green. Group-randomization designs. In *Encyclopedia of Biostatistics (Ed. D G Altman and E A Gehan, P Armitage and T Colton)*, pages 1781–1784. John Wiley and sons, London, 1998.
- [10] O Onwujekwe, E Shu, and P Okonkwo. Can community leaders’ preferences be used to proxy those of the community as a whole? *J Health Serv Res Policy*, 4:133–138, 1999.
- [11] P Dey, S Collins, M Desai, and C Woodman. Adequacy of cervical cytology sampling with the Cervex brush and the Aylesbury spatula: a population based randomised controlled trial. *Brit. Med. J.*, 313:721–723, 1996.
- [12] K P West, J Katz, S K Khattri, S C LeClerq, E K Pradhan, S R Shrestha, P B Connor, P Christian S M Dali, R P Pokhrel, and A Sommer. Double blind, cluster randomised trial of low dose supplementation with vitamin a or β carotene on mortality related to pregnancy in Nepal. *Brit. Med. J.*, 318:570–575, 1999.
- [13] A L Kinmonth, A Woodcock, S Griffin, N Spiegel, and M J Campbell. Randomised controlled trial of patient centred care of diabetes in general practice: impact on current wellbeing and future disease risk. *Brit. Med. J.*, 317:1202–1208, 1998.
- [14] J L Hutton. Ethics of medical research in developing countries: the role of international codes of conduct. *Stat. Meth. Med. Res.*, 9:185–206, 2000.
- [15] P R Williamson, J L Hutton, J Bliss, J Blunt, M J Campbell, and R Nicholson. Statistical review by research ethics committees. *J. R. Statist. Soc. A*, 163:5–13, 2000.
- [16] R E Ashcroft. Human research subjects, selection of. In *Encyclopedia of Applied Ethics (Ed. Chadwick, F)*, pages 627–639. Academic Press, San Diego, 1998.
- [17] C Snowdon, D Elbourne, and J Garcia. Zelen randomization: attitudes of parents participating in a neonatal clinical trial. *Con. Clin. Trials.*, 20:149–171, 1999.
- [18] I Chalmers and WA Silverman. Professional and public double standards on clinical experimentation. *Con. Clin. Trials.*, 8:388–391, 1987.
- [19] S J L Edwards, D A Braunholtz, R J Lilford, and A J Stevens. Ethical issues in the design and conduct of cluster randomised controlled trials. *Brit. Med. J.*, 318:1407–1409, 1999.
- [20] R E Ashcroft. Giving medicine a fair trial. *Brit. Med. J.*, 320:1686, 2000.
- [21] S J L Edwards, R J Lilford, D A Braunholtz, J Jackson, J Hewison, and J Thornton. Ethical issues in the design and conduct of randomised controlled trials. *Health Technology Assessment*, 2(15):vi+128, 1998.
- [22] K M Taylor, R G Margolese, and C L Soskolne. Physicians’ reasons for not entering eligible patients in a randomized clinical trial of surgery for breast cancer. *New Eng. J. Med.*, 310:1363–1367, 1984.
- [23] M Zelen. A new design for randomized clinical trials. *New Eng. J. Med.*, 300:1242–11245, 1979.
- [24] H.M. Thornton. Breast cancer trials: a patient’s viewpoint. *The Lancet*, 339:44–45, 1992.
- [25] P Toynbee. No one really wins in this life-and-death lottery. *The Independent*, May 25::15 (cols 1–7), 1996.
- [26] J L Hutton and R E Ashcroft. Some popular versions of uninformed consent. *Health Care Anal.*, 8:41–52, 2000.

- [27] S J L Edwards, R J Lilford, D Braunholtz, and J Jackson. Why “underpowered” trials are not necessarily unethical. *Lancet*, 350:804–807, 1997.
- [28] J L Hutton and P R Williamson. Bias in meta-analysis with variable selection within studies. *Appl. Statist.*, 49:359–370, 2000.
- [29] J L Schafer. *Analysis of incomplete multivariate data*. Chapman & Hall, London, 1997.
- [30] P Skrabanek. Why is preventive medicine exempted from ethical constraints? *J. Med. Ethics*, 16:187–190, 1990.
- [31] J L Hutton. Medical ethics and statistics. In *Encyclopedia of Biostatistics* (Ed. D G Altman, E A Gehan, P Armitage and T Colton), pages 2540–2546. John Wiley and sons, London, 1998.
- [32] S J Pocock. When to stop a clinical trial. *Brit. Med. J.*, 305:235–240, 1992.