

Cluster-randomised Trials in Nursing Research: An Overview, an Example, and some Recommendations

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Abstract

Background

It is commonly agreed in nursing research that interventions should be best evaluated in randomized trials. This is because only random allocation allows a valid measurement of the causal effect of the intervention under study. In general, individual patients are assigned randomly to intervention and control group in randomized trials. However, there are situations where it is preferable to assign clusters of individuals to intervention groups, resulting in “cluster-randomized” or “group-randomized” trials.

Methods

We explain and illustrate the specific problems of such trials by using an example from our own research and give some recommendations for conducting and reading cluster-randomized trials.

Results

The main consequence of a cluster-randomized design is that, unlike individually randomized trials, the outcome for each participant cannot be assumed to be independent from that of any other participant in the same cluster. Instead, participants in the same cluster are more likely to have similar outcomes. This lack of independence influences design, analysis and reporting of cluster randomized trials.

Conclusions

In general, individually randomized trials should be preferred to cluster-randomized trials. However, a cluster-randomised trial may be preferred if the intervention is applied naturally to groups, there is danger of contamination, or it is more cost-effective than an individually randomized trial. The cluster-randomised design should be beared in mind during all phases of trial conduction, especially in sample size calculation, analysis, and reporting.

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2 **Keywords:**

3 nursing research, cluster-randomized, group-randomized, intra-cluster-correlation,
4 mixed models
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9 **What is already known about the topic?**

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- 13 • In nursing research, interventions are increasing evaluated in cluster-
14 randomized trials.
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 - 16 • In cluster-randomized trials, the outcome for each participant cannot be
17 assumed to be independent from that of any other participant in the same
18 cluster. This influences design, analysis and reporting of cluster randomized
19 trials.
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27 **What this paper adds?**

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- 30 • In general, individually randomized trials should be preferred to cluster-
31 randomized trials. However, a cluster-randomised trial may be preferred if
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 - 33 ▪ the intervention is applied naturally to groups,
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 - 35 ▪ there is danger of contamination, or
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 - 37 ▪ it is more cost-effective than an individually randomized trial.
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 - 40 • The cluster-randomised design should be beared in mind during all phases of
41 trial conduction, especially in sample size calculation, analysis, and reporting.
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What is a cluster-randomized trial?

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4 It is commonly agreed in nursing research as well as in all other empirical sciences
5 that randomized controlled trials are the gold standard to evaluate interventions or
6 treatments. Randomization guarantees (at least in the long run) an equal distribution
7 of known and unknown prognostic or risk factors in intervention and control groups.
8 Differences in outcomes can thus be attributed solely to the intervention and not to
9 possible baseline differences. The randomized design is the only design in empirical
10 research that allows (without additional assumptions and except for truly random
11 imbalances) a valid assessment of causal intervention effects.
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14 In general, the single patient (or proband) is randomized to intervention or control
15 group. There are situations, however, where not single patients, but clusters (or
16 groups) of patients are randomized to intervention groups although outcomes are still
17 measured at the single patient level. These studies are called „cluster-randomized“ or
18 „group-randomized“ trials.
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21 Cluster-randomized designs gain increasing use in empirical sciences and also in
22 nursing research (Cox et al., 2008, Fossey et al, 2006, Jahn et al. 2009). There is an
23 extension of the CONSORT reporting guideline to cluster-randomized trials
24 (Campbell et al., 2004) and, in addition to the standard textbooks (Donner and Klar,
25 2000, Hayes and Moulton, 2009, Murray DM, 1998), there is a number of tutorial
26 papers (Christie et al. 2009, Ukoumunne et al. 1999, Wears, 2002) that offer a non-
27 technical access to these trials.
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When should we perform a cluster-randomized trial?

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31 Individually randomized trials should be preferred to cluster-randomized trials
32 because the former more probably yield equal distributions of prognostic or risk
33 factors on a patient level. There are, however, at least three situations where cluster-
34 randomized trial designs can (or even should) be preferred (Ukoumunne et al. 1999,
35 Wears, 2002).
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38 The first situation is where the intervention is applied naturally to groups, for example
39 when the effect of a new organisational form (common meal vs. individual meal) is
40 assessed in a nursing home. In this case all residents would have to participate in the
41 newly established form.
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The second situation occurs when there is the danger of contamination if an individually randomized trial is performed. Contamination refers to the possibility that patients from the intervention group might interact with members of the control group thus “contaminating” the control group with the intervention. This problem mostly occurs with educational interventions. Consider a training to prevent falls in nursing homes. It would be advantageous to randomize all residents from one nursing home to intervention or control group. Otherwise, residents randomized to the intervention group and receiving the training might communicate details of the intervention to residents randomized to the control group. The teachers for this preventive intervention are another potential source of contamination. Once trained in the teaching program, teachers might also share their knowledge with patients from the control group.

The third situation applies when a cluster-randomized trial is more cost-effective than an individually randomized trial. We consider again an educational intervention as an example. In most cases it would be more cost-effective to give the intervention in groups of participants than to teach each participant alone.

What is different in cluster-randomised trials?

The main difference between an individually and a cluster-randomized trial is that outcomes in the latter can not be considered independent. Patients educated by the same teacher or treated on the same ward will be more similar than patients from different teachers or wards. Two patients educated by a „good“ teacher tend to have „good“ results, two patients of a „bad“ teacher are expected to have “bad” results. In terms of wards, different wards generally foster patients with different diseases and different handicaps. Two critically ill patients from an oncological ward may react similar on an intervention (with an expected poor outcome) as compared to two less serious ill patients from a dermatological ward with expected better outcomes.

The resulting correlation between patients from the same cluster, the so called intra-cluster correlation (ICC), must be considered while both planning and analysing a cluster-randomised trial. As the common statistical methods are only valid for independent data, cluster-randomised trials call for more advanced statistical models. In most cases, the family of mixed (or hierarchical, or multilevel) models (Brown and Prescott, 2006) is used for analysis. Herein, the statistical model is extended by an

1 additional random effect for the different clusters thus adjusting for intra-cluster
2 correlation. These models have evolved a lot in recent years, are estimable with
3 standard software (SAS, Stata, or R), and extensions to non-continuous or more
4 complex hierarchical structures (e.g., additional repeated measurements in the time
5 course) are possible. We warn against the still common practice of aggregating
6 outcome information in clusters and continuing the analysis with the aggregated
7 outcomes. First, aggregation results in a needless loss of information. Second, the
8 statistical uncertainty from aggregating is generally ignored in further analyses,
9 rendering confidence intervals and p-values too small, thus feigning a level of
10 statistical confidence that does not exist.

11 The greatest challenge remaining with cluster-randomised trials is the prestudy
12 calculation of sample size. In addition to the prerequisites that are needed for sample
13 size calculation in an individually randomized trial, in a cluster-randomised trial it is
14 mandatory to have a good guess for the expected intra-cluster correlation coefficient
15 (ICC). A careful determination of the expected intra-cluster correlation is important
16 because the calculated sample size depends heavily on this value, with larger values
17 of the ICC enlarging the necessary sample size. Fortunately, ICCs from cluster-
18 randomised trials in nursing research are usually small. An analysis of 1.039 ICCs
19 from the adjacent area of primary care research (Adams et al., 2004) yielded a
20 median ICC of 0.01.

21 Furthermore, the sample size for a cluster-randomised trial depends on the number
22 of clusters even if the total number of patients is kept fixed. Ten patients in 100
23 clusters would give a larger statistical power to detect an intervention effect than
24 100 patients in 10 clusters. Thus, when planning a cluster-randomised trial it is preferable
25 to put more effort in recruiting additional clusters than in recruiting additional patients
26 within clusters. Putting it to extremes, a cluster-randomised trial with only two clusters
27 (one intervention and one control cluster) is useless as the intervention effect can not
28 be separated from the cluster effect; a cluster-randomized trial with one patient per
29 cluster reduces to an individually randomised trial.

30 Having only a limited number of clusters in the trial induces another potential
31 problem, namely that of imbalances of prognostic or risk factors in intervention and
32 control groups. This is a simple consequence of the fact that randomisation creates
33 similar intervention groups only in the long run. With only a small, finite number of
34 clusters (that is, "in the short run") the beneficial effect of randomization might not
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1 have yet been achieved and intervention and control group might remain with
2 relevant differences in important prognostic factors. One possible solution, already at
3 the design stage, to this problem is matching of clusters with similar properties and
4 performing the randomisation to intervention or control group within the matched
5 strata. Another solution is to adjust for baseline differences between intervention and
6 control clusters by statistical models. In this case, selection algorithms for covariates
7 should already be prespecified in the trial plan and derived from a subject-matter
8 view.
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16 **An example of a cluster-randomised trial**

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20 The authors were involved in planning and conducting two cluster-randomised trials,
21 one finished and published (Jahn et al., 2009), the other currently ongoing (Jahn et
22 al., 2010). We report here on some methodical details of the first trial, for complete
23 description of design and results we refer to the original paper (Jahn et al., 2009).
24 The aim of the trial was to reduce chemotherapy-induced anorexia, nausea, and
25 emesis (ANE) through a structured nursing intervention. The intervention was
26 evaluated in 208 cancer patients receiving chemotherapy with moderate to high
27 emetogenic potential on 14 wards (those representing the clusters) in two German
28 university hospitals. Additionally to standard antiemetic treatment, patients from the
29 intervention wards received the SCION program consisting of four modules: advisory
30 consultation, optimizing emesis prophylaxis, nutrition counselling, and relaxation.
31 Patients from the control group received standard antiemetic treatment and standard
32 care. The sample size calculation relied on an assumed intra-class correlation of
33 0.05. This resulted in a necessary sample size of totally 200 patients. Just for
34 comparison, a similarly powered individually randomised trial would have needed
35 only a total of 140 patients.
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49 The reasons for performing a cluster-randomised (instead of an individually
50 randomised) trial are obvious. To avoid contamination through patients by spreading
51 details of the intervention program to control patients, all patients from one ward had
52 to belong to the same intervention group. Moreover, all nurses from one ward had to
53 be in the same intervention group, first to assure a constant application of the
54 intervention program through the continuing shift changes, and second, to avoid
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contamination of other nurses that might not been instructed to apply the intervention.

Primary outcome was the group difference in ANE intensity assessed by the Common Terminology Criteria for adverse events (CTCAE, NCI-CTEP, 2003.) form during the first 5 days of the second chemotherapy cycle. As a secondary outcome we also assessed patients' knowledge of side effects where this was evaluated using a 100-mm visual analogue scale ranging from 0="insufficient" to 100="very good". A purely descriptive analysis without adjusting for the cluster effect (figure 1) points to a small superiority of the SCION intervention. Patients in the SCION group reported an average knowledge of side effects of 71.7 mm, those from the control group one of 64.2 mm. This difference of 7.5 mm with a 95% confidence interval of [2.2; 12.8] would be judged significantly different from 0 with a p-value of $p=0,006$ from a standard t-test. This analysis, however, does not adjust for the cluster-randomised design and an analysis with a mixed model yields an effect of 7.1 mm [95% CI: -2.0; 16.2], which is not longer significant at the 5% level ($p=0.11$). The estimated ICC was found to be 0.07 [95% CI: -0.05; 0.19]. The effect of the intervention is thus overestimated if the clustering is not taken into account.

Some recommendations for cluster-randomised trials

The following recommendations, following in essence Ukoumunne et al. (1999) and Wears (2002), should aid researchers in designing, but also in reading reports from cluster-randomised trials.

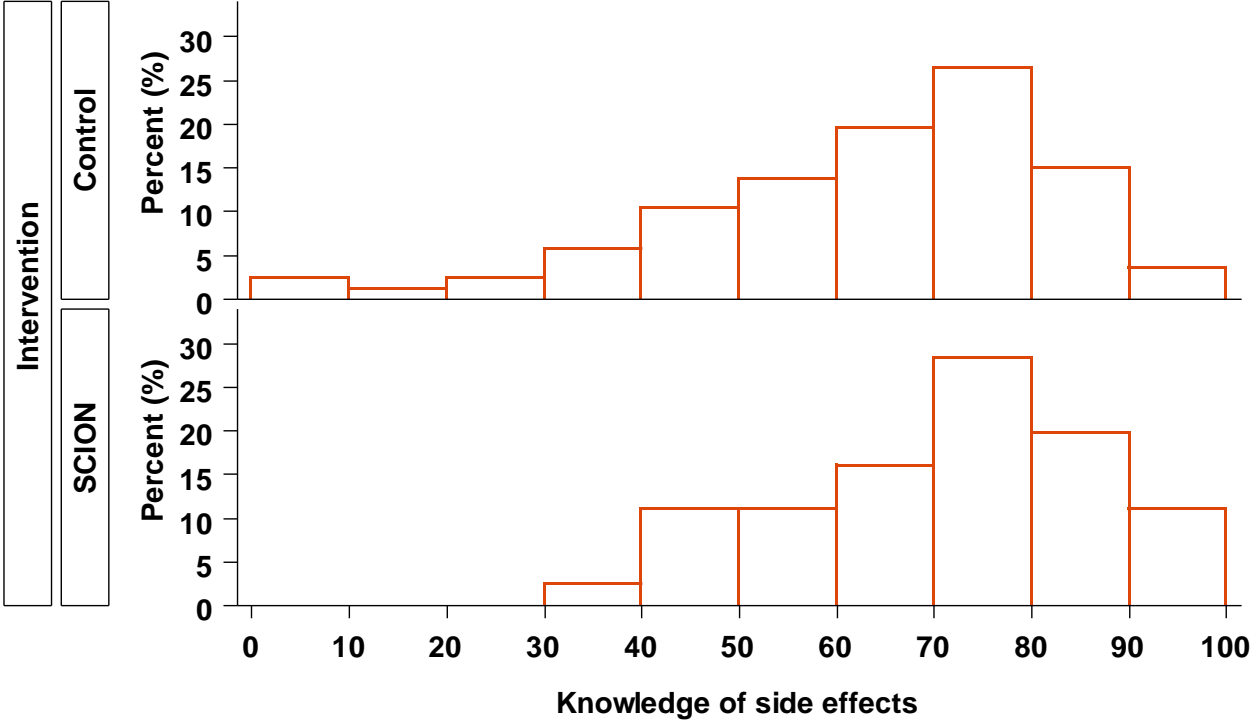
1. Individually randomized trials should be preferred to cluster-randomized trials. A solid justification for using a cluster-randomised design should thus be given and reasons for using it should be made explicit. A cluster-randomised trial may be preferred if
 - the intervention is applied naturally to groups,
 - there is danger of contamination, or
 - it is more cost-effective than an individually randomized trial.
2. The cluster-randomised design should be beared in mind during all phases of trial conduction, especially in sample size calculation, analysis, and reporting.
3. A sufficient number of clusters should be included. This facilitates to achieve similarity in intervention groups at baseline. Moreover, the statistical power of

1 a cluster-randomised trial depends more on the number of clusters than on the
2 number of individual patients. As a rule of thumb, we suggest that no cluster-
3 randomized trials should be performed with less than 10 clusters.
4

- 5 4. Consider a matching of clusters before randomisation. This is especially
6 important if there is only a small number of clusters available.
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- 8 5. Use the CONSORT-statement for cluster-randomised trials (Campbell et al.,
9 2004) when reporting your results. In particular, do not forget to give the
10 estimated values of intra-cluster correlation coefficients. This eases the
11 planning of future studies.
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Figure 1:

Descriptive summary (histograms) of the secondary outcome „Knowledge of side effects“ (100-mm visual analogue scale ranging from 0=“insufficient” to 100=“very good”) from the trial of Jahn et al (2009).



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