Cluster RCTs in CCM

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What is a Cluster RCT?

Cluster randomised trials are experiments in which clusters of individuals rather than independent individuals are randomly allocated to groups.
Cluster trial designs

- **Parallel cluster design**
  - Group 1: Baseline period, Decay period
  - Group 2: Intervention

- **Stepped-wedge design**
  - Step 0
  - Step 1
  - Step 2
  - Step 3
  - Step 4

- **Cross-over design**
  - Group 1: Wash-out period
  - Group 2: Analysis
  - Group 3
  - Group 4
Good reasons to do a cluster?

- To study interventions that are applied to groups of patients and not individuals
- To enhance subject compliance with intervention
- To avoid treatment group contamination
- Minimise selection bias (clinician selection or consent based)
- Ability to study individual and cluster level outcomes
Not so good reasons to do a cluster RCT

- Administrative convenience
- To obtain cooperation from investigators
- Ethical considerations
Stepped wedge

• Prior belief that the intervention will do more good than harm – ethics of exclusion
• Logistical, practical or financial constraints to simultaneous intervention
• Evaluating a public policy intervention that is being rolled-out before effectiveness demonstrated
• When you want to model the effect of time or length of intervention on effectiveness
Subgroups of cluster RCTs

The stepped wedge design

<table>
<thead>
<tr>
<th>Time periods</th>
<th>Participants/Clusters</th>
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<tbody>
<tr>
<td>1</td>
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<tr>
<td>2</td>
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<td>5</td>
<td>5</td>
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<tr>
<td>6</td>
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</tr>
</tbody>
</table>

Shaded cells represent intervention periods
Blank cells represent control periods
Each cell represents a data collection point
Methodological advantages of cluster RCT

• Enables RCT approach in situations where parallel design not possible
• Can model the effect of time of intervention on effectiveness
• Can model the effect of length of intervention on effectiveness
Methodological disadvantages of cluster RCT

- Limited ability to minimise baseline differences between groups
- Heterogeneity within and between clusters make analysis challenging (adjusted analysis)
- Blinding difficult (greater risk of bias)
- Cluster level education and implementation
- Requires extensive data collection, so best where routine data are to be used
Major disadvantage

- The inflation of power calculations
Can you do a power calc for my new cRCT?

I’ll need an alpha

I’ll need a beta

I’ll need a CER

I’ll need a delta

You will need 5831 patients

And now you have to multiply by the design effect

Yes, you now need 23,000 patients

p = 0.05

80%

50%

3%

WTF...

The what??????

#@&ξ
<table>
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<th></th>
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<tr>
<td>Alpha</td>
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<tr>
<td>Beta</td>
<td>80%</td>
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<tr>
<td>Delta</td>
<td>3.5%</td>
</tr>
<tr>
<td>Centres</td>
<td>25</td>
</tr>
<tr>
<td>Gamma</td>
<td>6,000</td>
</tr>
</tbody>
</table>
How do I calculate design effect?

- From the ICC
- Previous studies (poor)
- Existing high quality databases
- Datasets from previous RCTs
- Guess (very poor)
- Manipulate to drive study number down (very suspect)
Who is the research subject in cluster randomized trials in health research?

Andrew D McRae1,2,3*, Charles Weijer1,3,4, Ariella Binik3, Angela White3, Jeremy M Grimshaw5,6, Robert Boruch7, Jamie C Brehaut5,8, Allan Donner1,9, Martin P Eccles10, Raphael Saginur11, Merrick Zwarenstein12 and Monica Taljaard5,8

Abstract

This article is part of a series of papers examining ethical issues in cluster randomized trials (CRTs) in health research. In the introductory paper in this series, we set out six areas of inquiry that must be addressed if the CRT is to be set on a firm ethical foundation. This paper addresses the first of the questions posed, namely, who is the research subject in a CRT in health research? The identification of human research subjects is logically prior to the application of protections as set out in research ethics and regulation. Aspects of CRT design, including the fact that in a single study the units of randomization, experimentation, and observation may differ, complicate the identification of human research subjects. But the proper identification of human research subjects is important if they are to be protected from harm and exploitation, and if research ethics committees are to review CRTs.
The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials

Charles Weijer¹,²,³*, Jeremy M. Grimshaw¹,⁴,⁵, Martin P. Eccles⁶, Andrew D. McRae¹,³,⁷, Angela White¹, Jamie C. Brehaut⁴,⁸, Monica Taljaard¹,⁴,⁸, the Ottawa Ethics of Cluster Randomized Trials Consensus Group¹

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Introduction

Cluster randomized trials (CRTs), also known as group randomized, place-based, or community intervention trials, are increasingly important for the evaluation of interventions in health research [1–7]. In CRTs, groups, or “clusters”, of individuals—rather than the constituent individuals themselves—are randomly allocated to study arms, and outcomes are then measured on the individual cluster members. Examples of clusters include medical practices, hospital wards, schools, and communities. CRTs often evaluate complex or multifaceted interventions targeted at the cluster, professionals, or individual cluster members. (See Text S1 for a glossary of terms.)

CRTs pose distinct ethical challenges for several reasons. First, in CRTs the units of allocation, intervention, and outcome measurement may differ in a single trial. For example, in a CRT of teaching a new hand-washing technique to help avoid transmitting infection on hospital wards, the unit of allocation may be the hospital, the
Inadequate reporting of research ethics review and informed consent in cluster randomised trials: review of random sample of published trials

Monica Taljaard, scientist,1 Andrew D McRae, research director,2 Charles Weijer, professor,3 Carol Bennett, research coordinator,1 Stephanie Dixon, postdoctoral fellow,4 Julia Taleban, PhD candidate,4 Zoe Skea, research fellow,5 Martin P Eccles, professor,6 Jamie C Brehaut, scientist,1 Allan Donner, professor,4 Raphael Saginur, professor,7 Robert F Boruch, professor,8 Jeremy M Grimshaw, senior scientist1

ABSTRACT

Objectives To investigate the extent to which authors of cluster randomised trials adhered to two basic requirements of the World Medical Association’s Declaration of Helsinki and the International Committee of Medical Journal Editors’ uniform requirements for manuscripts (namely, reporting of research ethics review and informed consent), to determine whether the adequacy of reporting has improved over time, and to identify characteristics of cluster randomised trials associated with reporting of ethics practices.

Design Review of a random sample of published cluster randomised trials from an electronic search in Medline.

Setting Cluster randomised trials in health research.

Informed consent was sought, from whom consent was sought, and what consent was for.

INTRODUCTION

Cluster randomised trials are distinct from other randomised controlled trials in that the units of random assignment are intact clusters of entities such as entire medical practices, hospitals, schools, or communities, rather than the constituent individuals of these units themselves.1 The statistical implications of this hierarchical structure are well recognised, and an extensive literature exists to provide guidance for the appropriate design and analysis of these trials, but relatively little attention has been paid to the ethical...
Does clinical equipoise apply to cluster randomized trials in health research?

Ariella Binik¹, Charles Weijer¹,²,³*, Andrew D McRae¹,³,⁴, Jeremy M Grimshaw⁵,⁶, Robert Boruch⁷, Jamie C Brehaut⁵,⁸, Allan Donner³,⁹, Martin P Eccles¹⁰, Raphael Saginur¹¹, Monica Taljaard⁵,⁸ and Merrick Zwarenstein¹²

Abstract

This article is part of a series of papers examining ethical issues in cluster randomized trials (CRTs) in health research. In the introductory paper in this series, Weijer and colleagues set out six areas of inquiry that must be addressed if the cluster trial is to be set on a firm ethical foundation. This paper addresses the third of the questions posed, namely, does clinical equipoise apply to CRTs in health research? The ethical principle of beneficence is the moral obligation not to harm needlessly and, when possible, to promote the welfare of research subjects. Two related ethical problems have been discussed in the CRT literature. First, are control groups that receive only usual care unduly disadvantaged? Second, when accumulating data suggests the superiority of one intervention in a trial, is there an ethical obligation to act?

In individually randomized trials involving patients, similar questions are addressed by the concept of clinical equipoise, that is, the ethical requirement that, at the start of a trial, there be a state of honest, professional disagreement in the community of expert practitioners as to the preferred treatment. Since CRTs may not involve physician-researchers and patient-subjects, the applicability of clinical equipoise to CRTs is uncertain. Here we argue that clinical equipoise may be usefully grounded in a trust relationship between the state and research subjects, and, as a result, clinical equipoise is applicable to CRTs. Clinical equipoise is used to argue that control groups
What is the role and authority of gatekeepers in cluster randomized trials in health research?

Antonio Gallo¹,², Charles Weijer¹,³,⁴*, Angela White¹, Jeremy M. Grimshaw¹,⁵,⁶, Robert Boruch⁷, Jamie C. Brehaut⁵,⁸, Allan Donner¹,⁴,⁹, Martin P. Eccles¹⁰, Andrew D. McRae¹,⁴,¹¹, Raphael Saginur¹², Merrick Zwarenstein¹³ and Monica Taljaard¹,⁵,⁸

Abstract

This article is part of a series of papers examining ethical issues in cluster randomized trials (CRTs) in health research. In the introductory paper in this series, we set out six areas of inquiry that must be addressed if the CRT is to be set on a firm ethical foundation. This paper addresses the sixth of the questions posed, namely, what is the role and authority of gatekeepers in CRTs in health research? ‘Gatekeepers’ are individuals or bodies that represent the interests of cluster members, clusters, or organizations. The need for gatekeepers arose in response to the difficulties in obtaining informed consent because of cluster randomization, cluster-level interventions, and cluster size. In this paper, we call for a more restrictive understanding of the role and authority of gatekeepers. Previous papers in this series have provided solutions to the challenges posed by informed consent in CRTs without the need to invoke gatekeepers. We considered that consent to randomization is not required when...
The gate keeper

“Sorry, you’ll have to go back—they’re resuscitating you down there.”

“C’mon, c’mon—it’s either one or the other.”
Reports of cluster randomised trials require additional information to allow readers to interpret them accurately.

The effective reporting of randomised controlled trials has received useful attention in recent years. Many journals now require that reports conform to the guidelines in the Consolidated Standards of Reporting Trials (CONSORT) statement, first published in 1996 and revised in 2001. The statement includes a checklist of items that should be included in the trial report. These items are evidence based whenever possible and are regularly reviewed. The statement also recommends including a flow diagram to show the flow of participants from group assignment through to the final analysis.

The CONSORT statement focused on reporting parallel group randomised trials in which individual participants are randomly assigned to study groups. However, in some situations it is preferable to randomly assign groups of individuals (such as families or medical practices) rather than individuals. Reasons include the threat of contamination of some interventions (such as dietary interventions) if within clusters, known as the intracluster (or intraclass) correlation coefficient (ρ). The intracluster correlation coefficient is the proportion of the total variance of the outcome that can be explained by the variation between clusters. To retain power, the sample size should be multiplied by \(1+(m-1)ρ\), called the design effect, where \(m\) is the average cluster size. Hayes and Bennett describe a related coefficient of variation, \(k\), between clusters and Connelly considers an economic approach. Software is available to adjust for the intracluster correlation coefficient in an analysis.

The conduct of cluster randomised controlled trials may also differ from that of trials that randomise individuals. For instance, clusters are usually randomised all at once (or in batches) rather than one at a time. After randomisation, individuals in the clusters may be approached for consent, which raises the possibility of post-randomisation selection bias, or they may not, which raises ethical concerns. An expanded explanation of the methods of cluster randomised trials is available on the CONSORT website (www.consort-statement.org).
How do I read and interpret a cluster RCT?

With care!
Reading and interpreting a cluster RCT

- Did authors justify the use of a cluster design?
- Watch out for table 1! (baseline differences)
- Is the ICC and “ICC of convenience”? 
- How and when did randomisation occur
- Remember- lack of blinding when analysing outcomes
- Check analysis plan- make sure analysis adjusted
- Do outcomes refer to individual / cluster level / both
- How do you evaluate external validity?
Examples of cluster RCTs in CCM
Decontamination of the Digestive Tract and Oropharynx in ICU Patients

Decontamination of the Digestive Tract and Oropharynx in ICU Patients

STATISTICAL ANALYSIS
The original analysis plan, which specified in-hospital death as the primary end point, did not take into account analysis of cluster effects and failed to specify how to address imbalances in baseline characteristics between study groups. However, the study design did not preclude post-randomization selection bias. It was subsequently recognized that such an analysis plan failed to conform to the Consolidated Standards for the Reporting of Trials (CONSORT) guidelines for
Original Investigation  |  CARING FOR THE CRITICALLY ILL PATIENT

Effects of Decontamination of the Oropharynx and Intestinal Tract on Antibiotic Resistance in ICUs
A Randomized Clinical Trial

Evelien A. N. Oostdijk, MD, PhD; Jozef Kesecioglu, MD, PhD; Marcus J. Schultz, MD, PhD; Caroline E. Visser, MD, PhD; Evert de Jonge, MD, PhD; Einar H. R. van Essen, MD; Alexandra T. Bernards, MD, PhD; Ilse Purmer, MD; Roland Brimicombe, MD, PhD; Dennis Bergmans, MD, PhD; Frank van Tiel, MD, PhD; Frank H. Bosch, MD, PhD; Ellen Mascini, MD, PhD; Arjanne van Griethuysen, MD, PhD; Alexander Bindels, MD, PhD; Arjan Jansz, MD; Fred (A.) L. van Steveninck, MD, PhD; Wil C. van der Zwaet, MD, PhD; Jan Willem Fijen, MD, PhD; Steven Thijsen, MD, PhD; Remko de Jong, MD; Joke Oudbier, MD; Adrienne Raben, MD; Eric van der Vorm, MD, PhD; Mirelle Koeman, MD, PhD; Philip Rothbarth, MD, PhD; Annemieke Rijkeboer, MD; Paul Gruteke, MD; Helga Hart-Sweet, MD; Paul Peerbooms, MD, PhD; Lex J. Wissler, MD; Anne-Marie W. van Elsacker-Niele, MD, PhD; Kees Demmendaal, MD; Afke Brandenburg, MD, PhD; Anne Marie G.A. de Smet, MD, PhD; Marc J. M. Bonten, MD, PhD

IMPORTANCE  Selective decontamination of the digestive tract (SDD) and selective oropharyngeal decontamination (SOD) are prophylactic antibiotic regimens used in intensive care units (ICUs) and associated with improved patient outcome. Controversy exists regarding the relative effects of both measures on patient outcome and antibiotic resistance.
Introduction of the medical emergency team (MET) system: a cluster-randomised controlled trial

MERIT study investigators

Summary

Background Patients with cardiac arrests or who die in general wards have often received delayed or inadequate care. We investigated whether the medical emergency team (MET) system could reduce the incidence of cardiac arrests, unplanned admissions to intensive care units (ICU), and deaths.

Methods We randomised 23 hospitals in Australia to continue functioning as usual (n=11) or to introduce a MET system (n=12). The primary outcome was the composite of cardiac arrest, unexpected death, or unplanned ICU admission during the 6-month study period after MET activation. Analysis was by intention to treat.

Findings Introduction of the MET increased the overall calling incidence for an emergency team (3.1 vs 8.7 per 1000 admissions, p=0.0001). The MET was called to 30% of patients who fulfilled the calling criteria and who were subsequently admitted to the ICU. During the study, we recorded similar incidence of the composite primary outcome in the control and MET hospitals (5.86 vs 5.31 per 1000 admissions, p=0.640), as well as of the individual secondary outcomes (cardiac arrests, 1.64 vs 1.31, p=0.736; unplanned ICU admissions, 4.68 vs 4.19, p=0.599; and unexpected deaths, 1.18 vs 1.06, p=0.752). A reduction in the rate of cardiac arrests (p=0.003) and unexpected deaths (p=0.01) was seen from baseline to the study period for both groups combined.
A Multifaceted Intervention for Quality Improvement in a Network of Intensive Care Units
A Cluster Randomized Trial

Damon C. Scales, MD, PhD
Katie Dainty, MSc, PhD
Brigette Hales, MSc
Ruxandra Pinto, PhD
Robert A. Fowler, MDCM, MS
Neill K. J. Adhikari, MDCM, MSc
Merrick Zwarenstein, MBBCh, PhD

Despite expensive life-sustaining technologies, mortality and complication rates in critically ill patients remain high. Such patients should therefore receive all evidence-based practices. Unfortunately, eligible patients may not receive them. Community hospitals dedicated to intensive care often have limited resources.

Objective To determine the effectiveness of a multifaceted intervention to increase delivery of 6 evidence-based practices in community hospital ICUs.

Design, Setting, and Participants A pragmatic, cluster-randomized trial was conducted in 10 community hospital ICUs in Ontario, Canada. The study was conducted in 2 periods: a baseline monitoring period (November 2005 to October 2006) and an intervention period (December 2006 to August 2007).

Intervention We implemented a multifaceted intervention that included audit and feedback, expert-led educational sessions, and organizational support to improve delivery of 6 evidence-based practices. Due to resource limitations, only patients in one group received this intervention, whereas patients in the other group received usual care. Patients were randomly assigned to these groups in a 1:1 ratio.
Figure 1. Study Flow Diagram Showing Trial and Decay-Monitoring Period

15 ICUs

Group 1
7 ICUs

Phase 1
Prevention of VAP
(Control for Prophylaxis against DVT)

Pair 1 Care Practices
(4 months)

Phase 2
Prevention of CRBSI
(Control for Daily SBT)

Pair 2 Care Practices
(4 months)

Phase 3
Prevention of Decubitus Ulcers
(Control for Early Enteral Nutrition)

Pair 3 Care Practices
(4 months)

Phase 4
Prophylaxis against DVT

Pair 1 Care Practices
(3 months)

Phase 5
Daily SBT

Pair 2 Care Practices
(3 months)

Phase 6
Early Enteral Nutrition

Pair 3 Care Practices
(3 months)

Phase 2
Daily SBT
(Control for Prevention of CRBSI)

Phase 3
Early Enteral Nutrition
(Control for Prevention of Decubitus Ulcers)

Phase 4
Prevention of VAP

Phase 5
Prevention of CRBSI

Phase 6
Prevention of Decubitus Ulcers

Trial Period
12 months (Nov 2005 to Oct 2006)

Decay-Monitoring Period
9 months (Dec 2006 to Aug 2007)
An Intervention to Decrease Catheter-Related Bloodstream Infections in the ICU

Peter Pronovost, M.D., Ph.D., Dale Needham, M.D., Ph.D., Sean Berenholtz, M.D., David Sinopoli, M.P.H., M.B.A., Haitao Chu, M.D., Ph.D., Sara Cosgrove, M.D., Bryan Sexton, Ph.D., Robert Hyzy, M.D., Robert Welsh, M.D., Gary Roth, M.D., Joseph Bander, M.D., John Kepros, M.D., and Christine Goeschel, R.N., M.P.A.
<table>
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<tr>
<th>Variable</th>
<th>Incidence-Rate Ratio (95% CI)</th>
<th>P Value</th>
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<tr>
<td>Baseline</td>
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<tr>
<td>During implementation</td>
<td>0.76 (0.57–1.01)</td>
<td>0.063</td>
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<tr>
<td>After implementation</td>
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<tr>
<td>0–3 mo</td>
<td>0.62 (0.47–0.81)</td>
<td>0.001</td>
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<tr>
<td>4–6 mo</td>
<td>0.56 (0.38–0.84)</td>
<td>0.005</td>
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<tr>
<td>7–9 mo</td>
<td>0.47 (0.34–0.65)</td>
<td>&lt;0.001</td>
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<tr>
<td>10–12 mo</td>
<td>0.42 (0.28–0.63)</td>
<td>&lt;0.001</td>
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<tr>
<td>13–15 mo</td>
<td>0.37 (0.20–0.68)</td>
<td>0.001</td>
</tr>
<tr>
<td>16–18 mo</td>
<td>0.34 (0.23–0.50)</td>
<td>&lt;0.001</td>
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<tr>
<td>Teaching hospital</td>
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<tr>
<td>Bed size (per 100 beds)</td>
<td>1.03 (0.97–1.09)</td>
<td>0.33</td>
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‘Matching Michigan’: a 2-year stepped interventional programme to minimise central venous catheter-blood stream infections in intensive care units in England

THE MATCHING MICHIGAN COLLABORATION & WRITING COMMITTEE

ABSTRACT

Background: Bloodstream infections from central venous catheters (CVC-BSIs) increase morbidity and costs in intensive care units (ICUs). Substantial reductions in CVC-BSI rates have been reported using a combination of technical and non-technical interventions.

Methods: We conducted a 2-year, four-cluster, stepped non-randomised study of technical and non-technical (behavioural) interventions to prevent CVC-BSIs in adult and paediatric ICUs in England. Random-effects Poisson regression modelling was used to compare infection rates. A sample of ICUs participated in data verification.

Results: Of 222 ICUs in England, 215 (100 adult and 5 paediatric ICUs) participated in matching.

INTRODUCTION

Bloodstream infections (BSIs) from central venous catheters (CVCs) increase morbidity and are estimated to increase mortality risk by 25% and costs of care in the USA by US$16 550 on average per patient1 2 (box 1). A substantial body of evidence suggests that rates of CVC-BSIs are modifiable.3–13 The Michigan-Keystone project13 in 103 intensive care units (ICUs) in the USA reported a major reduction in CVC-BSIs from 7.7 to 1.4 CVC-BSIs per 1000 catheter days.
d: Adult ICU CVC-BSI rates by Cluster
Secular trends in Stepped wedge

Shaded cells represent intervention periods.
Blank cells represent control periods.
Each cell represents a data collection point.

Time periods
Participants/Clusters

5 4 3 2 1
1 2 3 4 5 6
Statistical Analysis

Because of its cluster randomized, double-crossover design, this study was conducted for a specific period and had no fixed sample size. The trial was partly performed to establish the feasibility of using a cluster randomized, double-crossover design to investigate fluid therapy in the ICU and, as there are no established statistical methodologies for prospectively determining sample sizes for cluster randomized, double-crossover studies with binary outcome variables, we did not perform sample size calculations.
Results of analysis of cRCTs in CCM (Cook et al)

- Half of studies failed to account for the effects of clustering when calculating sample size
- Studies rarely calculate the number of clusters and patients required to achieve a pre-specified effect size
- Blinding was poorly reported and limits the ability to assess the methodological quality of individual studies
- No consensus on appropriate analysis plan
Conclusions of analysis of cRCTs in CCM (Cook et al)

- Existing methods within cRCTs in CCM are often inadequate and do not reach the proposed standard
- Despite the CONSORT extension providing clearer guidance on how cRCTs should be conducted, greater clarity is still required
Conclusions

• cRCT must only be used in specific situations
• But they are very useful in these situations
• They have significant limitations and are often very large and expensive
• They are poorly performed and analysed in CCM