# Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preface</strong></td>
<td>xiii</td>
</tr>
<tr>
<td><strong>Acronyms and abbreviations</strong></td>
<td>xv</td>
</tr>
<tr>
<td>1 Introduction</td>
<td>1</td>
</tr>
<tr>
<td>1.1 Randomised controlled trials</td>
<td>1</td>
</tr>
<tr>
<td>1.1.1 Allocation at random</td>
<td>1</td>
</tr>
<tr>
<td>1.1.2 B-Blindness</td>
<td>2</td>
</tr>
<tr>
<td>1.1.3 C-Control</td>
<td>2</td>
</tr>
<tr>
<td>1.2 Complex interventions</td>
<td>3</td>
</tr>
<tr>
<td>1.3 History of cluster randomised trials</td>
<td>4</td>
</tr>
<tr>
<td>1.4 Cohort and field trials</td>
<td>4</td>
</tr>
<tr>
<td>1.5 The field/community trial</td>
<td>5</td>
</tr>
<tr>
<td>1.5.1 The REACT trial</td>
<td>5</td>
</tr>
<tr>
<td>1.5.2 The Informed Choice leaflets trial</td>
<td>6</td>
</tr>
<tr>
<td>1.5.3 The Mwanza trial</td>
<td>7</td>
</tr>
<tr>
<td>1.5.4 The paramedics practitioner trial</td>
<td>7</td>
</tr>
<tr>
<td>1.6 The cohort trial</td>
<td>8</td>
</tr>
<tr>
<td>1.6.1 The PoNDER trial</td>
<td>8</td>
</tr>
<tr>
<td>1.6.2 The DESMOND trial</td>
<td>9</td>
</tr>
<tr>
<td>1.6.3 The Diabetes Care from Diagnosis trial</td>
<td>10</td>
</tr>
<tr>
<td>1.6.4 The REPOSE trial</td>
<td>11</td>
</tr>
<tr>
<td>1.6.5 Other examples of cohort cluster trials</td>
<td>11</td>
</tr>
<tr>
<td>1.7 Field versus cohort designs</td>
<td>11</td>
</tr>
<tr>
<td>1.8 Reasons for cluster trials</td>
<td>12</td>
</tr>
<tr>
<td>1.9 Between- and within-cluster variation</td>
<td>14</td>
</tr>
<tr>
<td>1.10 Random-effects models for continuous outcomes</td>
<td>15</td>
</tr>
<tr>
<td>1.10.1 The model</td>
<td>15</td>
</tr>
<tr>
<td>1.10.2 The intracluster correlation coefficient</td>
<td>16</td>
</tr>
<tr>
<td>1.10.3 Estimating the intracluster correlation (ICC) coefficient</td>
<td>16</td>
</tr>
</tbody>
</table>
CONTENTS

1.10.4 Link between the Pearson correlation coefficient and the intraclass correlation coefficient 17
1.11 Random-effects models for binary outcomes 18
  1.11.1 The model 18
  1.11.2 The ICC for binary data 19
  1.11.3 The coefficient of variation 19
  1.11.4 Relationship between cvc and $\rho$ for binary data 20
1.12 The design effect 20
1.13 Commonly asked questions 21
1.14 Websources 21
  Exercise 22
  Appendix 1.A 22

2 Design issues 27
  2.1 Introduction 27
  2.2 Issues for a simple intervention 28
    2.2.1 Phases of a trial 28
  2.2.2 ‘Pragmatic’ and ‘explanatory’ trials 29
    2.2.3 Intention-to-treat and per-protocol analyses 29
    2.2.4 Non-inferiority and equivalence trials 30
  2.3 Complex interventions 30
    2.3.1 Design of complex interventions 30
    2.3.2 Phase I modelling/qualitative designs 32
    2.3.3 Pilot or feasibility studies 33
    2.3.4 Example of pilot/feasibility studies in cluster trials 33
  2.4 Recruitment bias 34
  2.5 Matched-pair trials 34
    2.5.1 Design of matched-pair studies 34
    2.5.2 Limitations of matched-pairs designs 36
    2.5.3 Example of matched-pair design: The Family Heart Study 36
  2.6 Other types of designs 37
    2.6.1 Cluster factorial designs 37
    2.6.2 Example cluster factorial trial 38
    2.6.3 Cluster crossover trials 38
    2.6.4 Example of a cluster crossover trial 39
    2.6.5 Stepped wedge 39
    2.6.6 Pseudorandomised trials 40
  2.7 Other design issues 41
  2.8 Strategies for improving precision 41
  2.9 Randomisation 42
    2.9.1 Reasons for randomisation 42
    2.9.2 Simple randomisation 43
    2.9.3 Stratified randomisation 43
    2.9.4 Restricted randomisation 43
    2.9.5 Minimisation 44
  Exercise 45
  Appendix 2.A 48
3 Sample size: How many subjects/clusters do I need for my cluster randomised controlled trial?

3.1 Introduction

3.1.1 Justification of the requirement for a sample size
3.1.2 Significance tests, $P$-values and power
3.1.3 Sample size and cluster trials

3.2 Sample size for continuous data – comparing two means

3.2.1 Basic formulae
3.2.2 The design effect (DE) in cluster RCTs
3.2.3 Example from general practice

3.3 Sample size for binary data – comparing two proportions

3.3.1 Sample size formula
3.3.2 Example calculations
3.3.3 Example: The Informed Choice leaflets study

3.4 Sample size for ordered categorical (ordinal) data

3.4.1 Sample size formula
3.4.2 Example calculations

3.5 Sample size for rates

3.5.1 Formulae
3.5.2 Example comparing rates

3.6 Sample size for survival

3.6.1 Formulae
3.6.2 Example of sample size for survival

3.7 Equivalence/non-inferiority studies

3.7.1 Equivalence/non-inferiority versus superiority
3.7.2 Continuous data – comparing the equivalence of two means
3.7.3 Example calculations for continuous data
3.7.4 Binary data – comparing the equivalence of two proportions

3.8 Unknown standard deviation and effect size

3.9 Practical problems

3.9.1 Tips on getting the SD
3.9.2 Non-response
3.9.3 Unequal groups

3.10 Number of clusters fixed

3.10.1 Number of clusters and number of subjects per cluster
3.10.2 Example with number of clusters fixed
3.10.3 Increasing the number of clusters or number of patients per cluster?

3.11 Values of the ICC

3.12 Allowing for imprecision in the ICC

3.13 Allowing for varying cluster sizes

3.13.1 Formulae
3.13.2 Example of effect of variable cluster size

3.14 Sample size re-estimation

3.14.1 Adjusting for covariates

3.15 Matched-pair studies

3.15.1 Sample sizes for matched designs
3.15.2 Example of a sample size calculation for a matched study
### Contents

3.16 Multiple outcomes/endpoints 73  
3.17 Three or more groups 74  
3.18 Crossover trials 74  
  3.18.1 Formulae 75  
  3.18.2 Example of a sample size formula in a crossover trial 75  
3.19 Post hoc sample size calculations 75  
3.20 Conclusion: Usefulness of sample size calculations 76  
3.21 Commonly asked questions 76  
  Exercise 77  
  Appendix 3.A 78

4 Simple analysis of cRCT outcomes using aggregate cluster-level summaries 83  
  4.1 Introduction 83  
    4.1.1 Methods of analysing cluster randomised trials 83  
    4.1.2 Choosing the statistical method 84  
  4.2 Aggregate cluster-level analysis – carried out at the cluster level, using aggregate summary data 84  
  4.3 Statistical methods for continuous outcomes 86  
    4.3.1 Two independent-samples t-test 86  
    4.3.2 Example 88  
  4.4 Mann–Whitney U test 91  
  4.5 Statistical methods for binary outcomes 94  
  4.6 Analysis of a matched design 95  
  4.7 Discussion 98  
  4.8 Commonly asked question 98  
  Exercise 99  
  Appendix 4.A 99

5 Regression methods of analysis for continuous outcomes using individual person-level data 102  
  5.1 Introduction 102  
  5.2 Incorrect models 104  
    5.2.1 The simple (independence) model 104  
    5.2.2 Fixed effects 104  
  5.3 Linear regression with robust standard errors 105  
    5.3.1 Robust standard errors 105  
    5.3.2 Example of use of robust standard errors 107  
    5.3.3 Cluster-specific versus population-averaged models 107  
  5.4 Random-effects general linear models in a cohort study 108  
    5.4.1 General models 108  
    5.4.2 Fitting a random-effects model 109  
    5.4.3 Example of a random-effects model from the PoNDER study 110  
    5.4.4 Checking the assumptions 110  
  5.5 Marginal general linear model with coefficients estimated by generalised estimating equations (GEE) 112  
    5.5.1 Generalised estimating equations 112  
    5.5.2 Example of a marginal model from the PoNDER study 113