UNIVERSITY OF PAVIA
Department of Brain and Behavioral Sciences

RESIDENZA UNIVERSITARIA BIOMEDICA
FONDAZIONE COLLEGIO UNIVERSITARIO S. CATERINA DA SIENA
Pro Multis Sapientia

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ADAPTIVE DESIGNS AND MULTIPLE TESTING PROCEDURES FOR CLINICAL TRIALS

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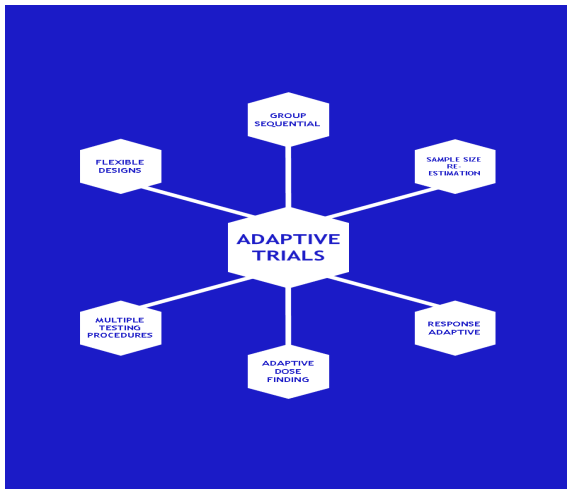

Michael Grayling is a postdoctoral researcher in the MRC Biostatistics unit (BSU), University of Cambridge. He works on adaptive trial design, with particular focus on single-arm trials and trials with clustering.

Adrian Mander is the director of the MRC BSU Hub for Trials Methodology Research. He works on methodology for adaptive trials with particular focus on dose-finding and dose-range studies. He has experience of trials methodology in both academic and industry setting.

David Robertson is a postdoctoral researcher in the BSU. He works on methodology for multiple testing in trials and adaptive designs, with particular focus on error rate control and statistical inference following an adaptive trial.

James Wason is a programme leader-track in the BSU and Professor of Biostatistics in Newcastle University. He works on methodology for adaptive trial design, with a particular focus on multi-arm trials and trials using biomarkers.

Clinical trials are the gold standard study design for assessing the efficacy and safety of an intervention. Adaptive designs are a novel approach to improving the efficiency and ethical properties of clinical trials. With an adaptive design, information gathered during the trial can be used to change the design in a statistically robust way. There are many types of adaptive designs that are possible for different situations ranging from phase I to phase III.

In both adaptive and non-adaptive trials, there are often multiple hypotheses being tested. Examples include trials with multiple endpoints, multiple treatment arms and when a trial tests a treatment in different patient subgroups. Adaptive trials often mean that a particular hypothesis is tested several times during the trial. This creates issues with multiple testing, for which suitable procedures are needed to ensure the appropriate error rate is controlled.

In this course we will give an overview of multiple testing issues and adaptive designs in trials. Throughout the course, real examples will be used to demonstrate the methodology. There will be a strong emphasis on learning how to use available software to implement the methodology in practice.

Program:

DAY 1: MULTIPLE TESTING PROCEDURES

- Introduction to multiple testing in trials

Reasons for multiplicity in trials - Types of error rate Simple corrections - *Practical*

- Advanced multiplicity correction

Hierarchical testing procedures - Closed testing procedures Graphical approaches - *Practical*

- Multiplicity correction in practice

Consideration of which methods should be used for which types of multiplicity issues - Case studies - Regulatory viewpoints - Available software - *Practical*

- Recap of day and time for general Q&A on multiple testing

DAY 2: ADAPTIVE DESIGNS

- Introduction to adaptive designs

Motivation - General concepts common to adaptive designs Frequentist vs Bayesian

- Phase I trials (1)

Introduction to the dose-escalation continual reassessment method (CRM) for single agents - Extensions to the CRM such as controlling overdosing and time to event - *Practical*

- Phase I trials (2)

Dose - escalation for combination products and specifically the PIPE methodology - Jointly considering efficacy and toxicity - *Practical*

- Single-arm designs

Design and analysis of single-stage single-arm trials - Design of two-stage single-arm trials (i.e., Simon's designs) - Extensions to Simon's framework (including adaptive two-stage designs) - Analysis of two-stage designs (p-value, point estimate, confidence intervals) - Advantages and disadvantages of single -arm designs relative to randomised designs - *Practical*

- Group-sequential and multi-arm multi-stage designs

History of group-sequential methods - Group-sequential methods for multi-arm trials - Multi-stage drop-the-loser designs - Adaptive randomisation for multi-arm trials - *Practical*

- Q&A

DAY 3: ADAPTIVE DESIGNS

- Dose ranging studies

Introduction to design issues when selecting optimal doses (including D-optimality) - Two-stage methods to handle uncertainty in parameter estimation - Dose selection that are robust to model choice

- Flexible designs

Unplanned adaptivity - p-value combination test - Conditional error rate

- Sample size re-estimation

Overview of the different types of sample size re-estimation - Blinded sample size re-estimation in randomised parallel arm trials - Sample size inflation factors and alpha adjustment procedures - Unblinded sample size re-estimation designs for bioequivalence trials - Computational exploration of sample size re-estimation designs - *Practical*

- Analysis after adaptive trials. Construction of confidence intervals

Median unbiased estimation - Bias-adjusted MLE Minimum variance conditionally unbiased estimation - *Practical*

- Practical issues in adaptive designs and future research

- Q&A and close

Venue

Residenza Universitaria Biomedica,
Fondazione Collegio Universitario S. Caterina da Siena
Via Giulotto, 12
27100 Pavia, Italy

Secretary

Dr. Gianfranca Corbellini,
Department of Brain and Behavioral Sciences
Pavia, Italy

REGISTRATION FEES

Academic	€ 400,00
Student	€ 300,00
Non academic	€ 450,00

Deadline for sending application

25 September 2017

Adaptive designs and multiple testing procedures for clinical trials

Deadline for sending application 25 September 2017

REGISTRATION FORM

The registration form, completed in all its part, must be sent to the secretary by email at dbbs.master@unipv.it together with the proof of payment.

Surname: .....

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Phone: ..... **Fax:** .....

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(ONLY FOR FOREIGN PEOPLE: copy of the passport for the invoice)

email: .....

Institution: .....

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Department: .....

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Qualification: .....

Under the Italian Law 196/2003, the personal data will be processed by the University of Pavia, Via Bassi 21, Pavia

REGISTRATION FEES	
Academic	**€ 400,00**
Student	**€ 300,00**
Non academic	**€ 450,00**

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