Bath M2P Workshop

Improving the Efficiency of Clinical Trials

From Methods to Practice

5 June 2025

University of Bath, BA2 7AY

Bath, UK

Bath M2P Workshop, 5 June 2025
Improving the Efficiency of Clinical Trials – from Methods to Practice
Location: The Wolfson Leture Theatre (4 West 1.7), University of Bath, UK

Organisers:
Dr Haiyan Zheng, Dr Peter Jacko

Agenda

Wednesday, 4 June 2025 [In-person only]

13:00 – 13:15	**Arrival**		
13:15 – 13:30	**Welcome & Introduction**		
13:30 – 15:45		Tutorial 1: A Primer on Statistical Designs for Modern Clinical Trials Tutorial 2: Principles of Simulation	
15:45 – 16:15	**Coffee/Tea and Refreshments**		
16:15 – 17:00		Speed Networking Session	
17:00 – 17:30	**Closing**		

Thursday, 5 June 2025 [In-person & Online]

9:00 – 9:50	**Arrival & Networking (Coffee, tea, pastry will be provided)**		
9:50 – 10:00	**Welcome**		
10:00 – 10:30	EP	**Elias Laurin Meyer** Berry Consultants	Designing a Seamless P1/P2a Open Enrollment CRM Dose Escalation Study
10:30 – 11:00	EP	**Lizzi Pitt** GlaxoSmithKline plc	Using Dynamic Programming to Produce Optimal First in Human Trial Designs
11:00 – 11:30	EP	**Zhi Cao** University of Cambridge	Robust Bayesian Hierarchical Models for Jointly Evaluating Toxicity and Efficacy in Basket Trials
11:30 – 12:00	EP	**Haiyan Zheng** University of Bath	Design and Analysis of Basket Trials Enabling Pairwise Borrowing of Information
12:00 – 13:00	**Lunch**		
13:00 – 13:30	SS	**Spotlight session** Early-career researchers	3-min Talk Each
13:30 – 14:00	CP	**Chris Jennison** University of Bath	Optimising Group Sequential and Adaptive Designs: Where Frequentist meets Bayes
14:00 – 14:30	CP	**Tom Parke** Berry Consultants	Using Machine Learning to Optimize Group Sequential Trial Design
14:30 – 15:00	CP	**Karim Anaya-Izquierdo** University of Bath	Spatial Spillover Effects in Cluster Randomised Trials: Lessons Learnt for Design
15:00 – 15:30	**Coffee/Tea and Refreshments**		
15:30 – 16:00	CP	**Nicolas Ballarini** Novartis AG	Optimizing Subgroup Selection in Two-stage Adaptive Enrichment and Umbrella Designs: An Insight into Theoretical Foundations and Practical Considerations
16:00 – 16:30	CP	**Peter Jacko** Lancaster University & Berry Consultants	A Fair and Efficient Randomization Scheme for Seamless Exploratory/Confirmatory Clinical Trials
16:30 – 17:00	PT	**Nick Berry** Berry Consultants	Getting the Most Out of Patient Data: Improving Efficiency in Adaptive Platform Trials Through Longitudinal Models
17:00 – 17:30	PT	**Tom Burnett** University of Bath	Adding Unplanned Treatments to Multi-Arm Multi-Stage Trials in Progress
17:30 – 17:45	**Closing & Networking**		

CP: Confirmatory Phase; EP: Early Phase; PT: Platform Trials; SS: Spotlight Session.

Attendance Map

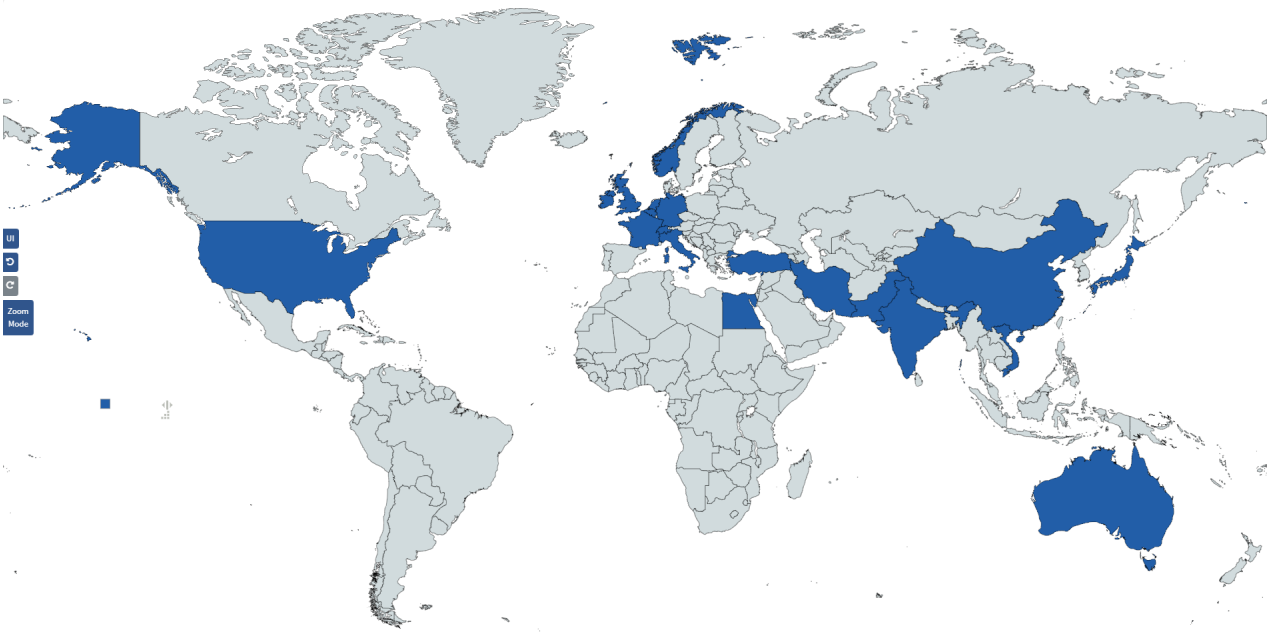


Figure 1. A worldwide view of the workshop audience.

Thank you once again for being such a crucial part of our event!

Talk Abstracts

Designing a Seamless P1/P2a Open Enrollment CRM Dose Escalation Study

Elias Laurin Meyer EP

Berry Consultants

Traditionally, phase I dose escalation designs aim to find the maximum tolerated dose (MTD), usually the highest dose whose probability to cause dose-limiting toxicities stays below a certain target toxicity level, and an adequate dosing scheme. In practice, however, focus on the MTD when selecting doses to take into registration trials often leads to exposing many trial participants to doses that either produce more toxicity without increased efficacy or severe toxicities that could both limit the options for receiving benefits or lead to premature discontinuation and missed opportunity for continued benefit. Recently, FDA launched Project Optimus with the aim of educating and innovating all stakeholders to, among other goals, move towards designing dose escalation trials that attempt to find "optimal" doses, where optimality comprises safety, tolerability and efficacy.

In this talk, we draw from our in-house experiences of designing first-in-human oncology trials to present a seamless phase 1 / phase 2a dose escalation design using open enrollment guided by the continual reassessment method (CRM) that evaluates both safety and efficacy. We introduce advanced CRM adaptations such as open enrollment, target toxicity intervals and escalation with overdose control, early stopping rules, backfilling and frontfilling, ad-hoc rules, etc., that not only vastly improve the performance and customizability of CRM, but also help identify "optimal" doses to take forward into registration trials. Finally, we discuss how to design and simulate such trials with the aid of targeted software and share insights on how to best communicate such designs with a clinical development team.

Using Dynamic Programming to Produce Optimal First in Human Trial Designs

Lizzi Pitt EP

GlaxoSmithKline plc

What is the best design for a First in Human trial? The answer depends on the aims and constraints of an individual trial.

Consider a trial conducted sequentially, allocating a dose to one cohort at a time. After observing results from one cohort, trial teams must decide which dose to give the next. We have developed a framework to make these decisions optimally. The key is fully specifying the aims of the trial up front: if you tell us what you want from the trial, we can find the optimal design for your specific trial.

We obtain optimal designs via dynamic programming. This requires calculations to be performed for every possible data set at each trial stage. Even with small sample sizes this state space is large, and prohibitively large when it comes to trials with a safety and an efficacy endpoint. We reformulate the state space as the space of posterior density functions for the dose-response model parameter and adapt the algorithm to a sample of this space. This produces a design that is a good approximation to the optimal rule. We can use the approximation to find an optimal design for a First in Human trial with both a binary efficacy endpoint and binary safety endpoint.

Different aims lead to different optimal rules, highlighting the importance of clearly defining the trial aims up front and choosing a design that meets those aims. This framework enables objective comparison of designs to find the optimal design for a specific trial.

Robust Bayesian Hierarchical Models for Jointly Evaluating Toxicity and Efficacy in Basket Trials

Zhi Cao

EP

University of Cambridge

Introduction: Phase II clinical trials focus primarily on establishing early efficacy of a new treatment, while the importance of continued monitoring toxicity cannot be ignored. In the era of precision medicine, basket trials have gained increasing attention, with biomarker-driven technology in various patient sub-populations sharing a common disease feature (e.g., genomic aberration). Thus, the borrowing of information across similar patient (sub-)groups is essential to expedite drug development.

Method: We propose a robust Bayesian hierarchical model [1] that can integrate and analyse clinically relevant differences in toxicity and efficacy, while accounting for possible patient heterogeneity and the correlation between the treatment and toxicity effects. From practical consideration, toxicity responses are treated as binary observations, and the efficacy outcomes are assumed to be normally distributed. Our model can be viewed as a two-dimensional extension of the exchangeable-nonexchangeable (EXNEX [2]) method: flexible weights are assigned to mixture distributions that imply different borrowing structures concerning toxicity and efficacy, namely, bivariate EX, bivariate NEX, EX in either toxicity or efficacy while NEX in the other.

Results & Conclusion: Compared with standard Bayesian hierarchical modelling and stand-alone analysis, simulation results of operating characteristics show that our models perform robustly in terms of (the Bayesian analogues of) type I error and power, especially when only toxicity effects are exchangeable (vice versa). The proposed method also has higher power than independently applying the EXNEX method to toxicity and efficacy treatment effects when they are obviously correlated and dissimilar.

Discussion: We give specific model recommendations for various clinical scenarios based on our simulation study of the joint evaluation of treatment effects. Possible future directions to our proposal are the sample size re-estimation and its implementation in dose-finding studies.

References

[1] Cao Z, Mozgunov P, Zheng H. (2025) Robust Bayesian hierarchical models for basket trials enabling joint evaluation of toxicity and efficacy. arXiv:2505.10317

[2] Neuenschwander B, Wandel S, Roychoudhury S, Bailey S. (2016) Robust exchangeability designs for early phase clinical trials with multiple strata. Pharmaceut. Statist., 15: 123–134.

Design and Analysis of Basket Trials Enabling Pairwise Borrowing of Information

Haiyan Zheng EP

University of Bath

Precision medicine goes beyond assessing whether a new treatment works on average to finding which subgroups of patients can benefit and to what extent. This talk will focus on basket trials, an innovative approach to precision medicine that simultaneously evaluates a new treatment in many disease (sub)types, for instance, colerectal cancer and breast cancer. Patients typically share a common disease feature (e.g., genetic aberration), on which the new treatment may improve the patient outcomes. Sophisticated analysis models for basket trials feature *borrowing of information* between subgroups (strata), which are preferred over the stand-alone analyses of the strata for higher power achieved to detect a treatment benefit. Methodology development of sample size determination for basket trials, however, appears to fall behind. A widely implemented approach is to sum up the sample sizes, calculated as if these trial subsets are to be carried out as separate studies.

In this talk, I shall introduce a class of Bayesian models [1,2] that characterise the complex data structure of basket trials. More specifically, this model reflects the concern that treatment effects in some strata may be more commensurate between themselves than with others. Closed-form sample size formulae can be derived to enable borrowing of information between commensurate strata [3,4]. Focus will then be shifted onto sample size reassessment based on interim estimates of pairwise commensurability of the stratum-specific treatment effects. Perspectives will be also given on the future methodology development for basket trial designs.

References

[1] Zheng H, Wason JMS. (2022) Borrowing of information across patient subgroups in a basket trial based on distributional discrepancy. Biostatistics, 23(1): 120-135.
[2] Ouma LO, Grayling MJ, Wason JMS, Zheng H. (2022) Bayesian modelling strategies for borrowing of information in randomised basket trials. Journal of the Royal Statistical Society: Series C, 71(5): 2014-2037.
[3] Zheng H, Jaki T, Wason JMS. (2023) Bayesian sample size determination using commensurate priors to leverage pre-experimental data. Biometrics (Biometric Methodology), 79(2): 669-683.
[4] Zheng H, Grayling MJ, Mozgunov P, Jaki T, Wason JMS. (2023) Bayesian sample size determination in basket trials borrowing information between subsets. Biostatistics, 24(4): 1000-1016.

Spotlight Session

Short talks by early-career researchers:

Luana Boumendil, University of Bath, UK
Daniel Burrows, University of Bath, UK
Neža Dvorsak, University of Bath, UK
Corey Voller, University of Bath, UK
Moka Komaki, Yokohama City University, Japan
Luke Ouma, AstraZeneca, UK
Stef Bass, University of Cambridge, UK
Jiyang Ren, AstraZeneca, China

Optimising Group Sequential and Adaptive Designs: Where Frequentist meets Bayes

Chris Jennison

CP

University of Bath

The search for efficient group sequential and adaptive designs poses interesting challenges. In confirmatory clinical trial, it is usual to require control of the type I error rate, or the familywise error rate when multiple hypotheses may be tested. Efficient trial designs should have good properties over a range of possible scenarios while meeting complex requirements on type I error and possibly on power too. I shall illustrate how frequentist and Bayes methods can be combined to find efficient solutions to clinical trial design problems. The talk will focus on early stopping through the use of group sequential tests. I shall comment briefly on applications to sample size modification, seamless Phase 2-3 trials with treatment selection, and adaptive enrichment trials.

Using Machine Learning to Optimize Group Sequential Trial Design

Tom Parke

CP

Berry Consultants

As trial designs become more complex, they gain parameters and thresholds that need to be set with no simple and obvious method of deriving them. Even for a group sequential trial (one of the oldest and simplest type of adaptive trial), choosing the number and timing of the interim, and the stopping parameter boundaries is largely a matter of custom and practice.

One of the problems of conventional optimization techniques such as simulated annealing and genetic algorithms is that they assume an exact result of evaluating the "function" at any particular set of parameter choices, but trying to optimize a clinical trial design will require simulation and have an approximate solution. Fortunately there are relatively new optimization techniques specifically for optimizing functions with approximate values (such as from simulation) that use Bayesian smoothing, and Python code libraries (in particular "botorch") that implement them.

We will present the results of an experiment in optimizing a group sequential trial design using such an approach.

Spatial Spillover Effects in Cluster Randomised Trials: Lessons Learnt for Design

Karim Anaya-Izquierdo

CP

University of Bath

TBD.

Optimizing Subgroup Selection in Two-stage Adaptive Enrichment and Umbrella Designs: An Insight into Theoretical Foundations and Practical Considerations

Nicolas Ballarini CP

Novartis AG

We design two-stage confirmatory clinical trials that use adaptation to find the subgroup of patients who will benefit from a new treatment, testing for a treatment effect in each of two disjoint subgroups. Our proposal allows aspects of the trial, such as recruitment probabilities of each group, to be altered at an interim analysis. We use the conditional error rate approach to implement these adaptations with protection of overall error rates. Applying a Bayesian decision-theoretic framework, we optimize design parameters by maximizing a utility function that takes the population prevalence of the subgroups into account. We show results for traditional trials with familywise error rate control (using a closed testing procedure) as well as for umbrella trials in which only the per-comparison type 1 error rate is controlled. We present numerical examples to illustrate the optimization process and the effectiveness of the proposed designs.

A Fair and Efficient Randomization Scheme for Seamless Exploratory/Confirmatory Clinical Trials

Peter Jacko CP

Lancaster University & Berry Consultants

Multi-arm and platform clinical trials designed to seamlessly govern arm selection and arm confirmation bring administrative and operational benefits compared to separate trials for each phase, which would normally need to wait for the selection (Phase II) trial to fully complete for all arms (doses, treatments, etc.) before starting to design and set up a confirmatory (Phase III) trial. They also have a potential for inferential benefits, where data from the earlier phase may be used to, e.g.: strengthen the control dataset by using non-concurrent controls, speed up the start of the confirmatory trial, build a longitudinal model for the outcomes allowing for interim decisions, etc. Response-adaptive methods such as permanent arm dropping (using futility thresholds) or temporary arm dropping (updating randomization ratios) are often used in order to more effectively use patient resources, to more effectively treat trial participants, and to identify better arms more rapidly. A downside of seamless trials is the potential estimation bias when pooling data from the two phases with different randomization ratios. A downside of response-adaptive methods is the sponsors' concern that, if early data is unfavourable, their arm may not enrol the desired number of participants or to enrol at the desired rate. We present a novel randomization scheme which is not only operationally and inferentially seamless but also allocationally seamless, as both phases of each arm start when the arm joins the trial. It delivers the desired fairness properties between the arms as well as mitigates the estimation bias by keeping the randomization ratio constant for the data to be used in the final analysis of the confirmatory trial.

Getting the Most Out of Patient Data: Improving Efficiency in Adaptive Platform Trials Through Longitudinal Models

Nick Berry PT

Berry Consultants

Interim stopping rules for efficacy or futility—including group sequential, goldilocks, and promising zone frameworks—enable trial decisions prior to reaching maximum enrollment targets. Such designs reduce anticipated sample sizes while preserving statistical power and controlling type I error rates. Response-adaptive randomization, arm elimination, and related allocation strategies have received extensive investigation and widespread implementation. These adaptive allocation approaches concentrate randomization efforts to gather additional data on promising treatment arms. Such methodologies are broadly adopted and represent state-of-the-art departures from traditional clinical trial information utilization paradigms. A frontier that has similar goals as the previously mentioned adaptations, but has not been the focus of as much research as the other two is the use of early endpoint data in adaptive decision making. It's a seemingly obvious statistical observation that a well-designed clinical trial should use all data available to it to make decisions. Despite that, it is common to ignore early data about subjects in a clinical trial, often to the extent that only subjects with complete information are included in statistical models.

This talk will focus primarily on the statistical efficiencies gained in adaptive clinical trials that include intermediate endpoint values in the estimation of the final endpoint through multiple imputation. The early data augments the data from completely observed subjects to increase the effective sample size of the analysis population – this sample size improvement is quantifiable. The increased effective sample size leads to improved precision and MSE of the treatment response estimates at the final endpoint time. This precision benefit increases power over a design that only uses completers. Additionally, incorporating longitudinal data in the analysis models produces interim estimates nearer to the estimates available after complete data is available on the subjects enrolled at the interim. Leveraging early endpoint data, and its relationship to the final endpoint, leads to more accurate predictive probabilities, which results in better decision making at interim analyses.

The statistical efficiencies are presented in the context of a Phase III trial with multiple active doses, arm dropping, and a long time to endpoint. Discussion of relevant FDA guidance documents, and FDA response to using multiple imputation in a Phase III trial will be integrated into the talk.

Adding Unplanned Treatments to Multi-Arm Multi-Stage Trials in Progress

Tom Burnett PT

University of Bath

Multi-arm multi-stage (MAMS) platform trials efficiently compare several treatments with a common control arm. Crucially MAMS designs allow for adjustment for multiplicity if required. If for example, the active treatment arms in a clinical trial relate to different dose levels or different routes of administration of a drug, the strict control of the family-wise error rate (FWER) is paramount. Suppose a further treatment becomes available, it is desirable to add this to the trial already in progress; to access both the practical and statistical benefits of the MAMS design. In any setting where control of the error rate is required, we must add corresponding hypotheses without compromising the validity of the testing procedure.To strongly control the FWER, MAMS designs use pre-planned decision rules that determine the recruitment of the next stage of the trial based on the available data. The addition of a treatment arm presents an unplanned change to the design that we must account for in the testing procedure. We demonstrate the use of the conditional error approach to add hypotheses to any testing procedure that strongly controls the FWER. We use this framework to add treatments to a MAMS trial in progress. Simulations illustrate the possible characteristics of such procedures.

End of Workshop.

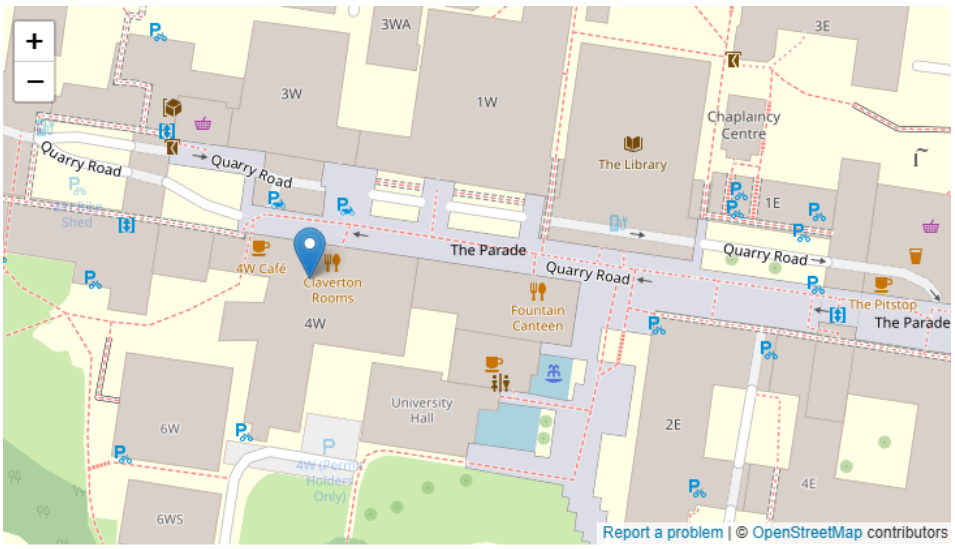
Useful Information

This workshop will be held at the **Wolfson Lecture Theatre (4W1.7)**, Department of Mathematical Sciences, University of Bath.

Pastries, coffee, tea, biscuits, luncheons will be offered according to the schedule.

Wi-Fi will be available during the workshop. Delegates can use the 'WiFi Guest' network.

How to get to the Wolfson Lecture Theatre on campus?



Wolfson Lecture Theatre (4W1.7)
4 West
University of Bath
Claverton Down
Bath
BA2 7AY
United Kingdom

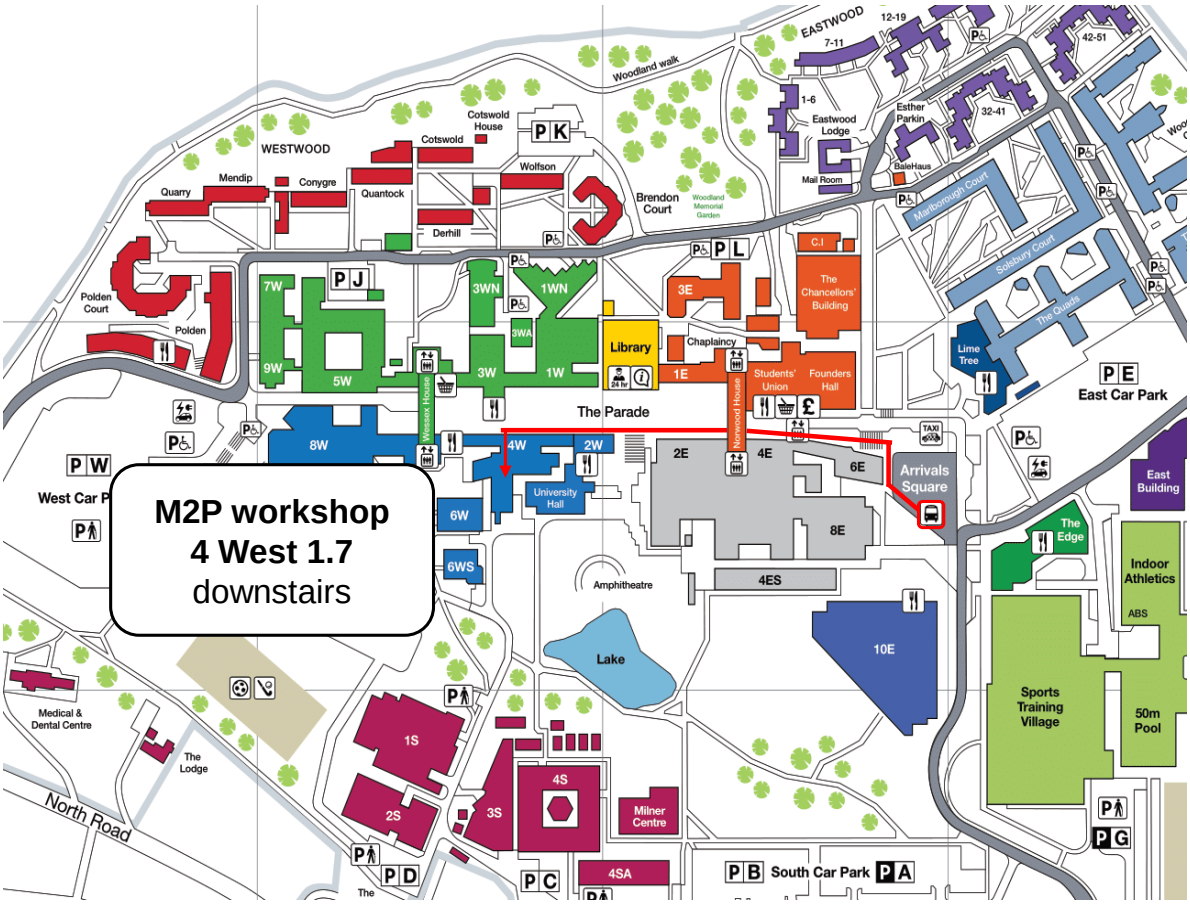
- **Rail:** Bath Spa railway station is 10-15 minutes away by bus (U1 Unibus; Departure: Dorchester Street; Destination: Arrivals Square *on campus*; see the next page for reaching 4W1.7 from the Arrivals Square). Taxis are available from the railway station at most times.

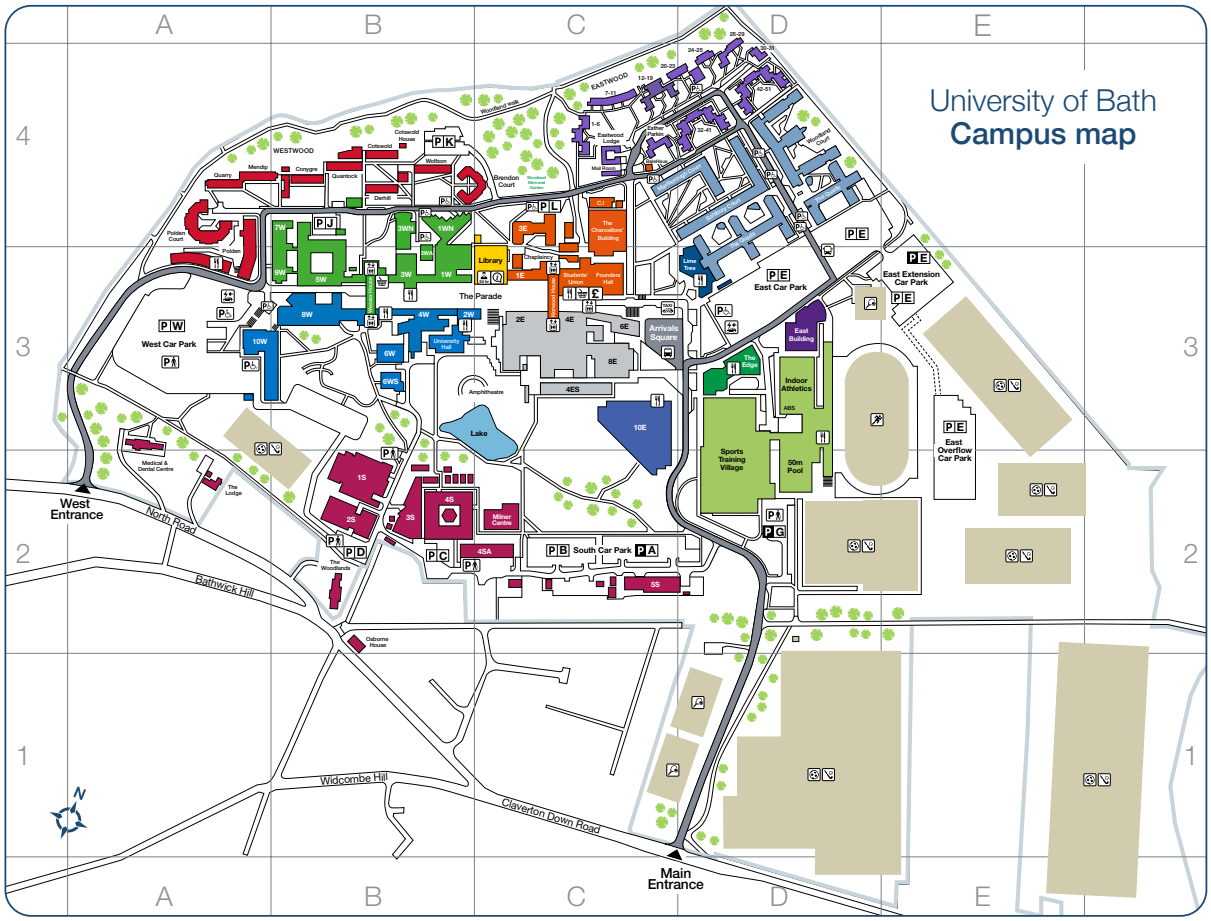
- **Coach:** Bath's coach station is next door to the railway station.

- **Car:** If you are using a satnav, use 'Norwood Avenue, Bath', not 'Quarry Road', to get to the main entrance of the campus and visitor car parks. You can also search for 'admiral.salads.ages' on `https://what3words.com/admiral.salads.ages`. There are several city centre car parks; more information: `https://www.bathnes.gov.uk/find-car-parks-bath`

Find out more about getting to the city of Bath and the University campus: `https://www.bath.ac.uk/guides/travelling-to-the-city-of-bath/`

From Arrivals Square to Workshop Venue





Key

	Building	Grid Ref.
4 West Café	4 West (4W)	B3
Advancement Office	2 South (2S)	B2
Applied Biomechanics Suite	ABS	D3
Architecture & Civil Engineering	6 East (6E), 4 East South (4ES)	C3
Bakeaway	3 West (3W)	B3
Bale Haus	BH	C4
Bus Stop	Arrivals Square	C3
CAFÉ at Polden (Summer vacation only)	Polden	A3
CAFÉ at The Edge (Functions only)	The Edge	D3
Campus Infrastructure	C.I	C4
Careers Centre	WH 2.24	B3
Central Stores	5 South (5S)	C2
Chancellors' Building		C4
Chaplaincy Centre	CC	C3
Chemical Engineering	9 West (9W)	B3
Chemistry	1 South (1S), 3 South (3S)	B2
Claverton Rooms	2 West (2W)	B3
Communications	Wessex House (WH)	B3
Computer Science	1 West (1W), 3 West (3W)	B3
Cotswold House		B4
Dental Centre		A3
Doctoral College	10 West (10W)	A3
East Accommodation Centre	Woodland Court	D4
Economics	3 East (3E)	C4
The Edge Arts	The Edge	D3
Education	1 West North (1WN)	B4
Electronic & Electrical Engineering	2 East (2E)	C3
Founders Hall		C3
Fountain Canteen	2 West (2W)	B3
Fresh Grocery Store	Wessex House (WH)	B3
Goods Received	5 South (5S)	C2
Health	1 West (1W)	B3
	6 West South (6WS)	B3
Human Resources	Wessex House (WH)	B3
IMI (The Institute for Mathematical Innovation)	4 East South (4ES)	C3
International	10 West (10W)	A3
IT Help Desk	Library	C3
Landscape	5 South (5S)	C2
Library		C3
Life Sciences Biology & Biochemistry	4 South (4S)	B2
Pharmacy & Pharmacology	5 West (5W)	B3
	7 West (7W)	B4
Lime Tree	The Quads	D3
Mail Room	Eastwood	C4
Management (School of)	10 East (10E)	C3
	The Edge	D3

	Building	Grid Ref.
The Market	Students' Union (SU)	C3
Marketing	Wessex House (WH)	B3
Mathematical Sciences	4 West (4W), 6 West (6W)	B3
Mechanical Engineering	4 East (4E), 8 East (8E)	C3
Medical Centre		A3
The Milner Centre for Evolution		C2
Muslim Prayer Room	Norwood House	C3
Natural Sciences	3 South (3S)	B2
Norwood House		C3
Nursery	Westwood	B4
Parade	2 West (2W)	B3
Physics	8 West (8W)	B3
Pitstop	Students' Union (SU)	C3
Plug Bar	Norwood House	C3
Politics, Languages & International Studies	1 West North (1WN)	B4
Post Office (in Fresh Grocery Store)	Wessex House (WH)	B3
Postgraduate Admissions	Wessex House (WH)	B3
Print Services	8 West (8W)	B3
Psychology	10 West (10W)	A3
Reception	Library	C3
Research & Innovation Services	Wessex House (WH)	B3
Security	Library	C3
Social & Policy Sciences	3 East (3E)	C4
Sports Café	Sports Training Village (STV)	D3
Sports Training Village	Sports Training Village (STV)	D3
Starbucks	Students' Union (SU)	C3
Student Centre	Students' Union (SU)	C3
Student Finance	Wessex House (WH)	B3
Student Parcel Room	Eastwood Lodge	C4
Student Support - The Roper Centre	4 West (4W)	B3
Students' Union	Students' Union (SU)	C3
Students' Union Offices	Students' Union (SU)	C3
Swimming Pool	Sports Training Village (STV)	D2
Taxi Rank	Arrivals Square	C3
The Tub	Students' Union (SU)	C3
Undergraduate Admissions & Outreach	Wessex House (WH)	B3
University Hall	2 West (2W)	B3
Vice-Chancellor's Office	4 West (4W)	B3
Wessex House (WH)		B3
West Accommodation Centre	Polden	A3
Woodland Memorial Garden		C4
The Writing Centre	6 East (6E)	C3

Accommodation	Grid Ref.
Brendon Court	B4
Eastwood	C4,D4
Marlborough Court	C4
Norwood House	C3
Osborne House	B2
Polden	A3
Polden Court	A4
Solsbury Court	D4
The Lodge	A2
The Quads	D4
Westwood	A4, B4
Woodland Court	D4

- Bus stop
- Coach Drop Off Point
- Taxi Rank
- Food & Drink
- Shopping
- ATM
- Lift
- Sports pitches
- Athletics track
- Tennis courts
- 24 hour security
- University Reception

The Campus is built around the main Parade which forms a central spine with Norwood House at the east end and Wessex House at the west end. The Library and Learning Centre is the University's central hub and all buildings are identified according to their east/west position in relation to it. Odd numbers in building names indicate that they are located on the northern side of the Parade, on the same side as the Library, and even numbers are on the southern side. The main pedestrian Parade is Level 2.

Please note that all University buildings, the Parade and the underdeck are smoking free areas.

Car Parking

Visitor car parking - Pay & Display: East Extension, A and G. The East car park provides a wheelchair and accessible approach to the Parade and a drop off point by 1WN also provides wheelchair access to the Parade.

Host Institution & Industry Partners

This workshop is part of the STEEP research programme, funded by Cancer Research UK through Dr Zheng's Career Development Fellowship (RCCCDF-May24/100001).

Department of
Mathematical Sciences

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NOVARTIS

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