The Institute of Cancer Research

PHD STUDENTSHIP PROJECT PROPOSAL:

PROJECT DETAILS	
Project Titles:	1. Statistical Issues in Design and Analysis of Platform Trials in Cancer 2. Development of Innovative Adaptive Designs to Improve Efficiency in Early Phase Clinical Trials
SUPERVISORY TEAM	
Primary Supervisor(s):	Christina Yap
Associate Supervisor(s):	Judith Bliss (both Projects) James Wason (Project 1) Adrian Mander (Project 2)
DIVISIONAL AFFILIATION	
Primary Division:	Clinical Studies
Primary Team:	Clinical Trials and Statistics Unit

PROJECT PROPOSAL

BACKGROUND TO THE PROJECT – please decide on either Project 1 or 2 when applying for this studentship

Project 1 - Statistical Issues in Design and Analysis of Platform Trials in Cancer

Here, the student will focus on improving design and analysis of adaptive platform trials in cancer. Traditionally, a trial will assess a new intervention treatment (often compared with the standard care) one at a time. However this is time-consuming and costly. Adaptive platform trials, on the other hand, allow for a more efficient strategy of evaluating several therapies for one (or more) diseases concurrently, and accept additions of new treatment arms or patient population during the trial [1]. Adaptive features could be implemented at the interim assessments, such as dropping of futile treatments, steering patients towards better performing treatments [2], or enriching a specific subgroup of patients who might benefit from the treatment better. Such designs indisputably can provide efficiency improvements, statistically or operationally or both.

This work will be motivated by ongoing adaptive platform trials in cancer to assess several interesting methodological issues, such as the use of reliable short-term outcomes, decision criteria, sharing of control information, response-adaptive randomisation and pooling of information across arms using Bayesian techniques. There will be opportunities for the newly developed efficient methodologies to be applied to existing trials, as well as to influence the design and analysis of future such trials.

References

[1] Renfro, L. A., and D. J. Sargent. "Statistical controversies in clinical research: basket trials, umbrella trials, and other master protocols: a review and examples." *Annals of Oncology* 28.1 (2016): 34-43.

[2] Yap, C., Lin, X., & Cheung, Y. K. K. (2015). Sequential Elimination in Multi-Arm Selection Trials. *Modern Adaptive Randomized Clinical Trials: Statistical and Practical Aspects*, *81*, 411-426, edited by Sverdlov, A (ed)

Project 2 - Development of Innovative Adaptive Designs to Improve Efficiency in Early Phase Clinical Trials

There is a great need to accelerate patients' access to innovative medicines and medical technologies, via rapid assessment of the safety and efficacy of new drugs. Adaptive designs enable the use of accruing data to modify aspects of an ongoing trial without compromising the validity of conclusions. Such innovative designs when used appropriately can provide efficiencies which can include smaller sample sizes, more efficient treatment discovery processes, increased chance of correctly answering the clinical question of interest and allocating more patients to better treatments.

In many early phase multi-stage clinical trials in oncology, decisions to drop an arm for excessive toxicity or futility at interim looks, is based on the probability of a binary event(s), toxicity and/or response, defined in terms of occurrence of such events within a defined assessment period. Repeated recruitment suspension after a set number of patients have been recruited at each stage, might be necessary to assess patient outcomes for such outcome-adaptive methods. If the assessment period for the outcomes is long, this would lead to impractical, extended trial duration whilst awaiting patients' outcomes. Often in practice, recruitment is however continuous and patients whose outcomes have not reached the full assessment period will be ignored in the interim analysis, which leads to a waste of valuable information.

Based on a real-world trial, one of the key aims is to develop an efficient design, utilising both complete and partial information of binary outcomes at each interim assessment. The design will be tailored to the trial's specific features and simulations will take into account how such design will be conducted in practice.

The other key focus of this project is to assess similarities and differences in frequentist and bayesian inferences that have been readily applied in early phase II adaptive trials, and to develop bias-adjusted priors that can be used for estimation after using a Bayesian adaptive design to maintain similar estimates to likelihood-based analysis.

References

[1] Pallmann P, Bedding AW, Choodari-Oskooei B, *et al.* Adaptive designs in clinical trials: why use them, and how to run and report them. *BMC Med* 2018;16:29. doi:10.1186/s12916-018-1017-7

[2] Cai, C., Liu, S., & Yuan, Y. (2014). A Bayesian design for phase II clinical trials with delayed responses based on multiple imputation. *Statistics in medicine*, *33*(23), 4017-4028.

[3] Yap C and Cheung YK (2018). Sequential elimination in multi-arm multi-stage selection trials. Wiley StatsRef: Statistics Reference Online https://doi.org/10.1002/9781118445112.stat08024

[4] Yap C, Pettitt A and Billingham L (2013): Screened selection design for randomised phase II oncology trials: an example in chronic lymphocytic leukaemia. BMC Med Res Methodol. 2013; 13: 87.

PROJECT AIMS (up to 5 bullet points)

PROJECT 1

(1) Conduct a literature review of methodology used in adaptive platform trials in cancer
(2) Based on ongoing or published platform trials, identify key areas where efficiency in the design and/or analysis could be improved
(3) Develop efficient methodologies (such as sharing of control information, pooling of information across arms, flexible decision criteria) tailored to the trial specific features.

PROJECT 2

(1) Literature review on current early phase methodology that can incorporate delayed outcomes in toxicity and/or efficacy
(2) Based on a real-world dose-finding trial, develop an efficient adaptive design to accommodate trial specific features with delayed outcomes
(3) Compare and contrast Frequentist early phase adaptive designs with comparable Bayesian designs
(4) Develop bias-adjusted priors that can be used for estimation after using a Bayesian adaptive design to maintain similar estimates to likelihood-based analyses.

RESEARCH PROPOSAL (max. 1000 words) Please provide information on the approaches to be used and the expected outcomes**.**

PROJECT 1

- Review statistical designs and analysis approaches used in platform trials in cancer
- Based on ongoing/published platform trials, identify key areas where efficiency in the design and/or analysis could be improved
- Using real-world case studies of platform trials, develop and investigate efficient methodologies tailored to the trial specific needs. This could include the use of reliable short-term outcomes, decision criteria, sharing of control information, response-adaptive randomisation and pooling of information across arms using Bayesian techniques. Simulations will be used to assess the efficiency gain compared to conventional approaches.
- Open access software may be created to allow researchers to implement proposed methodologies for future trials.

It is envisaged that the output from this work will provide new insights for the statistical and clinical community in the recommended methods for future design and analyses of platform trials.

Outputs: At least 3 peer reviewed publications are anticipated in both clinical and methodological journals. The first manuscript will describe the review and identify key gaps. The second and third will describe efficient methodologies that could be applied to two platform trials, and investigate the efficiency gain via simulations. A further software paper will be produced if applicable.

PROJECT 2

This project will comprise of two main components:

Phase I/II:

- Develop a novel Phase I/II adaptive design for evaluating efficacy and toxicity with delayed outcomes, motivated by a real-world cancer trial.
    - Simulations will be conducted to assess the operating characteristics of the proposed design in an ideal setting where patients can be enrolled as they become available, as well as to take into account practical constraints of trial conduct to determine the more realistic benefits of such adaptive designs when applied in practice.
- This PhD will also provide an excellent opportunity to work closely with clinical investigators on an early phase cancer trial to create a trial design tailored to the specific needs of the trial and implement it in practice.

Phase II:

- Comparison of commonly used Frequentist adaptive designs with comparable Bayesian Designs, comprising of single arm trials, randomised selection trials as well as multi-arm multi-stage trials
- Assess the pros and cons of using Frequentist and Bayesian approaches
- One of the key aims is to engage with non-statisticians to communicate the differences between the two different inference frameworks and to provide an easy digestible paper for the trial community.

Outputs: At least 3 peer reviewed publications are anticipated in both clinical and methodological journals. The first manuscript will describe the literature review, and the proposed trial design to utilise complete and partial information of binary responses at interim assessments. The second will describe the similarities and differences of the commonly used early phase II adaptive designs, using Frequentist and Bayesian approaches. The third will describe the development of bias-adjusted priors.

CANDIDATE PROFILE

Note: the ICR's standard minimum entry requirement is a relevant undergraduate Honours degree (First or 2:1)

Pre-requisite qualifications of applicants: e.g. BSc or equivalent in specific subject area(s)	2:1 or higher Honours degree in Mathematical Sciences including a statistical component in Statistics. A Master's degree in a quantitative discipline would also be desirable.
Intended learning outcomes: Please provide a bullet point list (maximum of seven) of the knowledge and skills you expect the student to have attained on completion of the project.	- The student will work in a high-quality environment of clinical trials and will be exposed to practical challenges that are often encountered - Ability to explain complex statistical methods to clinicians. - Ability to implement complex statistical analyses in R/STATA