Institution: University of Bath		
Unit of Assessment: B10 Mathematical Sciences		
Title of case study: Improving Clinical Trials by Innovative Statistical Design		
Period when the underpinning research was undertaken: 2000 - 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Christopher Jennison	Professor of Statistics	1985 – present
Period when the claimed impact occurred: 2014 - 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Many hundreds of clinical trials are conducted every year, each involving hundreds, sometimes thousands, of patients. These trials are expensive, with costs as high as GBP30,000 per patient. Research at University of Bath on group sequential monitoring and adaptive design has improved the conduct of clinical trials, leading to:

- faster results: making effective new treatments available sooner or stopping negative trials early;
- smaller sample sizes: average reductions of 20 - 30% in sequential trials;
- methods to modify trials while retaining statistical validity: this flexibility can accelerate the drug development process.

The impact of this research is economic (the business performance of pharmaceutical companies and businesses that support them), societal (enhancing public health and changing the policies adopted by regulators), and ethical (ensuring clinical trials remain safe, while bringing life-saving treatments into clinical use as rapidly as possible).

2. Underpinning research

While many research groups worldwide have contributed to the field of clinical trial design, the series of contributions by Jennison at University of Bath has been distinctive, influential and widely applied. The underpinning research can be summarised under three headings.

(i) Sample size modification in group sequential and adaptive clinical trials [1,2,3]

Articles [1], [2] and [3] concern rules for early stopping and sample size modification in clinical trials. Paper [1] challenges the philosophy of certain adaptive designs in which a trial's sample size is modified in response to interim estimates of the treatment effect. The results in [2] quantify the maximum savings that group sequential testing can achieve, enabling a definitive comparison of adaptive and non-adaptive designs. Paper [3] applies statistical decision theory to sample size modification and develops adaptive procedures that offer an efficient alternative to non-adaptive group sequential tests.

(ii) Application of group sequential tests to meta-analyses [4]

Article [4] discusses the relation between multi-stage combination tests used in adaptive designs for a single clinical trial and methods for combining data in the meta-analysis of a

number of different studies. The results in that paper have implications for both adaptive designs and a sequential approach to meta-analysis.

(iii) Adaptive designs for a survival endpoint [5]

Adaptive designs enable innovation in clinical trials, such as the data-driven selection of one of several dose levels during the course of a study, or deciding whether to focus attention on a patient subgroup in which the new treatment shows a more substantial effect. The combination test of Bauer and Köhne (*Biometrics*, 1994) is a key to many adaptive designs but it is well known that applying this method to survival endpoints can inflate the type I error rate. The new form of combination test defined in [5] solves this important and longstanding problem, facilitating the application of adaptive designs in studies with a survival endpoint.

(iv) Audit sampling [6]

Article [6] describes an application of sequential analysis that reduces the substantial cost associated with the independent central review of diagnoses of disease progression. The cost of such reviews in a large clinical trial can be millions of pounds. In the audit sampling approach, a random sample of diagnoses is assessed and, where sufficient agreement is observed between local and central decisions, no further assessment is needed.

The above research was carried out by Jennison at University of Bath, where he has been Professor of Statistics since 1993. Items [1], [2], [3] and [4] were written in collaboration with Professor Bruce Turnbull of Cornell University, USA; [5] and [6] are joint work with statisticians at AstraZeneca, UK.

3. References to the research

1. Jennison, C & Turnbull, BW 2003, 'Mid-course sample size modification in clinical trials based on the observed treatment effect', *Statistics in medicine*, vol. 22, no. 6, pp. 971-993. https://doi.org/10.1002/sim.1457

2. Jennison, C & Turnbull, BW 2006, 'Adaptive and nonadaptive group sequential tests', *Biometrika*, vol. 93, no. 1, pp. 1-21. https://doi.org/10.1093/biomet/93.1.1

3. Jennison, C & Turnbull, BW 2015, 'Adaptive sample size modification in clinical trials: start small then ask for more?', *Statistics in medicine*, vol. 34, no. 29, pp. 3793-3810. https://doi.org/10.1002/sim.6575

4. Jennison, C & Turnbull, BW 2005, 'Meta-analyses and adaptive group sequential designs in the clinical development process', *Journal of Biopharmaceutical Statistics*, vol. 15, no. 4, pp. 537-558. https://doi.org/10.1081/bip-200062273

5. Jenkins, M, Stone, A & Jennison, C 2011, 'An adaptive seamless phase II/III design for oncology trials with subpopulation selection using correlated survival endpoints', *Pharmaceutical Statistics*, vol. 10, no. 4, pp. 347-356. https://doi.org/10.1002/pst.472

6. Stone, A, Macpherson, E, Smith, A & Jennison, C 2015, 'Model free audit methodology for bias evaluation of tumour progression in oncology', *Pharmaceutical Statistics*, vol. 14, no. 6, pp. 455-463. https://doi.org/10.1002/pst.1707

4. Details of the impact

Jennison has promoted the impact of his research by communicating results to practitioners. Since August 2013, he has given 6 short courses (from half a day to 2 days) on group sequential and adaptive methods at international conferences, at companies, or to

professional societies. He has also applied his research expertise in clinical trial design in consultancy for companies including AstraZeneca, Beigene, Roche, Sanofi and Takeda. These activities have led to the following impact.

(i) Impact of group sequential and adaptive designs on clinical trial practice

Reference (A) describes the GATSBY trial conducted by Hoffman-La Roche to study drug therapies for advanced gastric cancer. Two forms of experimental treatment were compared to the control and, at an interim analysis, one experimental treatment was selected for comparison with the control in the remainder of the study. The interim analysis took place in October 2013, patient recruitment continued until January 2015, and the study concluded in October 2015. The adaptive nature of this trial, with treatment selection and a survival endpoint, required use of the new form of combination test defined in [5] to guarantee the crucial property that type I error is controlled unequivocally. The Statistical Analysis section of (A) states:

> *"A one-sided inverse normal combination test was used to compare overall survival between the treatment groups, with a correction for the interim treatment selection due to the adaptive seamless design[26]"*

where the citation "26" is to our paper [5].

Reference (B) describes the TAPPAS clinical trial, launched in January 2017, which studies treatments for patients with advanced angiosarcoma. The adaptive trial design incorporates population enrichment and sample size re-estimation. The report notes the dilemma that interim decisions should be based on all available data but, in doing so, the type-1 error could be inflated. The paper states:

> *"Recognizing this dilemma, Jenkins et al. [8] suggested a novel approach that would permit full use of all data available at the time of the interim analysis, including from patients who are censored for PFS"*

where the reference [8] is to our paper [5], and the methods we proposed were applied, enabling the trial to be conducted in an efficient and statistically sound manner.

Reference (C) describes the SELECT-1 clinical trial which ran between October 2013 and June 2016 investigating the addition of the inhibitor Selumetinib to chemotherapy for patients with advanced lung cancer. The primary endpoint in this study was progression-free survival and diagnoses of progression were reviewed to assess concordance between investigator assessments and blinded independent central review. Following the approach of [6], a random sample of scans was performed:

> *"A random selection of scans from 220 patients were also assessed by blinded independent central review, which agreed with investigative site review … in more than 80% of cases, and analyses of ascertainment bias supported the consistency of the results based on investigative site review and blinded independent central review[16]".*

Given the consistency of results in the sample, the expense of an exhaustive review was avoided. Here the citation "16" is to our paper [6].

Reference (D) concerned the assessment of cell therapy trials for heart disease in two Cochrane reviews. The Cochrane Library contains high-quality, systematic reviews that inform healthcare decision-making. The two reviews addressed two clinical outcomes: all-cause mortality and hospitalization for heart failure; and left ventricular ejection fraction. The authors describe potential pitfalls for meta-analyses when there is repeated statistical testing

in multiple meta-analyses over time, and their reviews follow the method of Trial Sequential Analysis (TSA). They write [D]:

> *"In this method [TSA], futility boundaries, originally designed for interim analyses of RCTs [Randomised Clinical Trials], are utilized to supply a threshold for "no effect" [33,34]"*

where citations "33" and "34" are to our papers [1] and [4]. They state [D]:

> *"Here we present the first study that assesses the clinical evidence using cumulative data from meta-analyses and TSA".*

and conclude [D]:

> *"Although the required meta-analyses IS [Information Size] have not been reached, there seems to be evidence that cell therapies reduce the risk of mortality and rehospitalization for HF when administered to HF patients".*

Thus, this application of our research has informed policy for the use of cell therapy in treating heart disease and also created procedures for use in further Cochrane Reviews that will inform other areas of healthcare decision-making.

(ii) Economic benefits to producers of statistical software [Cytel]

Cytel's *East* software for the design and analysis of sequential trials draws on Jennison's work, in particular articles [3] and [5]. In the letter **(E)** the President of Cytel states:

> *"Cytel has grown dramatically … with annual revenues increasing from $27,000,000* [USD27,000,000] *in 2013 to over $200,000,000* [USD200,000,000] *in 2020. Our flagship software package East© is the industry standard. It is used by almost all major pharmaceutical companies (e.g., GSK, Novartis, Pfizer, Merck, Amgen, Lilly, Genentech), numerous smaller pharma and biotech companies and governmental agencies (e.g., FDA, NIH).*
>
> *A heavily used module in East© is the "Survival Module" for the design and interim monitoring of trials with mortality endpoints. The methodology implemented in East©, for adaptive survival trials in which the patient enrollment and treatment is based on predictive biomarkers, relies crucially on the theory published by Jenkins, Stone and Jennison (2011). This paper has had a major impact on oncology trials. Such trials no longer enroll large numbers of patients based on a general histological cell type, but focus instead on smaller subgroups of patients whose tumors conform to a specific biomarker status within the histological cell type. This has resulted in bringing many new oncology drugs to market and has thereby benefitted cancer patients whose genetic mutations are targeted by the new drugs. We, at Cytel, have used the results of the Jenkins, Stone and Jennison (2011) paper for the design of the TAPPAS trial of angiosarcoma.*
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> *Another key module in East© concerns "Sample Size Re-estimation". In developing new methods that extend the "Promising Zone" approach of Mehta and Pocock (2011), we have been influenced greatly by the proposals of Jennison and Turnbull (2015) which provide a gold-standard for what can be achieved. … these approaches are currently being utilized by Cytel's strategic consulting group as they design adaptive designs for their clients".*

(iii) Impact of research into group sequential and adaptive design on policy

Research at Bath has shaped policy of the US Food and Drug Administration. The FDA publishes "Guidances" which pharmaceutical companies should follow if their products are to be submitted for approval in the US. Our methods have informed FDA policy on the design of group sequential and adaptive clinical trials.

The FDA guidance for industry **(F)** on "Adaptive Design Clinical Trials for Drugs and Biologics" of November 2019 cites [5] as methodology for adaptive survival trials. As noted above, the key contribution of our work is that it enables adaptive designs to be used with a survival or other time-to-event endpoint, while still protecting the type I error rate.

The FDA guidance **(G)** on "Adaptive Designs for Medical Device Clinical Studies" of July 2016 cites [2] for its analysis of methods for sample size re-assessment.

5. Sources to corroborate the impact

(A) Thuss-Patience, P.C. et al. (2017) Trastuzumab emtansine versus taxane use for previously treated HER2-positive locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (GATSBY): an international randomised, open-label, adaptive, phase 2/3 study. *Lancet Oncology*, 18, 640–53. https://doi.org/10.1016/S1470-2045(17)30111-0

(B) Mehta, C.R., et al. (2019) An adaptive population enrichment phase III trial of TRC105 and pazopanib versus pazopanib alone in patients with advanced angiosarcoma (TAPPAS trial). *Annals of Oncology*, 30, 103-108. https://doi.org/10.1093/annonc/mdy464

(C) Jänne, P.A., et al. (2017) Selumetinib plus docetaxel compared with docetaxel alone and progression-free survival in patients with KRAS-mutant advanced non–small cell lung cancer: The SELECT-1 randomized clinical trial. *Journal of the American Medical Association*, 317,1844-1853. https://doi.org/10.1001/jama.2017.3438

(D) Fisher, S.A., e al. (2016) Cell therapy for heart disease: trial sequential analyses of two Cochrane reviews. *Clinical Pharmacology and Therapeutics*, 100, 88-101. https://doi.org/10.1002/cpt.344

(E) Letter from President and co-founder of Cytel (producers of the East© software package), 15 December 2020.

(F) U.S. FDA, "Adaptive Design Clinical Trials for Drugs and Biologics: Guidance for Industry", November 2019. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry

(G) U.S. FDA, "Adaptive Designs for Medical Device Clinical Studies: Guidance for Industry and FDA staff", July 2016. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-designs-medical-device-clinical-studies