TEACHING CLINICAL TRIAL DESIGN AND MANAGEMENT USING AN ONLINE VIRTUAL ENVIRONMENT

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ABSTRACT

Providing pharmaceutical science students relevant and authentic work-related experience in conducting clinical trials is difficult within the constraints of a university course. Students undertaking courses in the design and management of clinical trials cannot experiment on humans due to practical and ethical reasons. This study evaluates the use of an online virtual environment, called the *Island*, as a method for overcoming these limitations by giving students the opportunity to conduct clinical trials in a virtual world. In this study, the *Island* was integrated into tutorial and projects for a course in clinical trial design and management. *Island*-based tutorials were used to demonstrate, apply, reinforce and assess understanding of clinical trial concepts covered in lectures. The *Island* was also used for project-based work where students designed a clinical trial, developed a research proposal, conducted the trial using the *Island*, wrote up a research report and participated in a clinical audit. This paper describes the integration of the *Island* into the clinical trial course and evaluates students' perceptions of its implementation. The major strengths and limitations of the implementation are discussed. The authors conclude that delivering future courses without the use of the *Island* would be difficult to conceive.

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INTRODUCTION

Clinical trials are experiments performed on human subjects and are a major component in the development of new medicines and other medical treatments. The Pharmaceutical Education Council's (PEC) report on skill gaps in the pharmaceutical and biopharmaceutical industries found that Australian university graduates are ill-equipped to take on clinical trial role-related tasks within the industry (PEC, 2008). Practical (time, resources and cost) and ethical limitations imposed on university courses restrict the authentic and work-relevant practical components of clinical trial design and management courseware. Thus, there is a current need to provide relevant and work-related training to pharmaceutical science students for future work in the clinical trials industry.

One such course at RMIT University which covers the design and management of clinical trials aims to meet this need. However, practical and ethical issues present many challenges in delivering authentic, work-relevant learning experiences for pharmaceutical science students enrolled in the course. While it is possible to conduct class experiments, the intrusive nature of clinical trials presents challenges. For example, a class experiment investigating the effect of caffeinated sport drinks using students enrolled in the course as participants raises ethical issues. There is also the issue of forcing students to focus on one topic that may or may not be of interest to them. There is no doubt that removing these limitations would help improve student engagement and learning outcomes.

A possible solution to these issues in the teaching and learning of the clinical trials came in the form of an online virtual environment developed by Bulmer (2005, 2010, 2011). Bulmer's creation, named the *Island*, is a virtual population of human inhabitants which enables students to conduct their own open-ended scientific studies without the practical and ethical limitations imposed by a university. The theory of learning behind the *Island* may be viewed from an experiential learning perspective where learning is defined as "the process by which knowledge is created through the transformation of experience" (Kolb, 1984, p. 38). Therefore, the *Island* is based on the assumption that learning is enhanced by doing or "experiencing" the content being delivered.

There are many examples of virtual simulators being used to enhance learning in a wide variety of disciplines including statistics (Neumann, Neumann, & Hood, 2011), public health (Spinello & Fischbach, 2004), ecology (Stafford, Goodenough, & Davies, 2010), physiology (Dobson, 2009), and

biology (Lin & Lehman, 1999). While the idea of simulating clinical trials is not new to the clinical trial industry (Holford, Kimko, Monteleone, & Peck, 2000), the application of clinical trial simulation for educational purposes has been limited. While Bulmer (2010) reported overall positive student experiences using the *Island* in large introductory statistics courses, no research has reported on using the *Island* in other applied science courses. Therefore the aim of this study was to evaluate the integration of the online virtual environment, the *Island,* into the teaching and learning of a course in clinical trial design and management.

THE *ISLAND*

The *Island* is accessed via a secured website hosted by the University of Queensland. The *Island* interface is very much like a website, but behind which hides a very complex computer simulation running in real time. The *Island* consists of a virtual online world of inhabitants known as "Islanders". The founding story behind the simulated population is that the Islanders settled on the *Island* following a shipwreck in 1779. After 240 years, the simulated population has grown to over 8000 people with approximately 15,000 Islanders having existed (both living and dead) over this period. Each Islander has a unique name, personal history and virtual 3D model (Bulmer, 2005). The *Island* itself is divided in 39 villages, each with a number of different regions made of up separate households. Each household is the home of one or more Islanders. Students can navigate around the *Island* between towns, regions and homes to find participants for scientific research (Figure 1).

The *Island* allows a large number of different study designs to be implemented across a broad range of topics. Surveys, observational designs and experiments are the primary focus. The inclusion of over 200 different independent and dependent variables, referred to as *tasks*, allows a large degree of open-endedness to potential research topics. Examples of these variables include the administration of caffeine drinks, paracetamol, diazepam, blood cholesterol readings, and body weight measurements. The interactions between variables are based on mathematical models built into the background of the *Island* to ensure a high degree of realism. For example, the *Island* includes a model which simulates the effect of adrenaline on the sympathetic nervous system (e.g. increased heart rate, breathing and blood pressure).

The *Island* is well suited for learning clinical trials as students can experience the process of designing a clinical trial, recruiting virtual Islanders to their study, randomly assigning Islanders to conditions, manipulating treatment variables to perform an experiment and collecting data to analyse the effect of the treatment. The *Island* also presents students with practical and ethical issues related to clinical trials. Sample size, informed consent, timing of treatments, inclusion/exclusion criteria, selecting an appropriate statistical analysis, drop-outs, and missing data all naturally arise during the experience of conducting a clinical trial on the *Island*.

THE CLINICAL TRIAL DESIGN AND MANAGEMENT COURSE

The clinical trial design and management course runs over one semester and covers eight topics related to clinical trials: epidemiology, biostatistics, randomisation, phases of clinical trials in drug development, ethics, good clinical research practice, statistical power and misconduct and reporting of clinical trials. The topics make up the weekly lecture content and coincide with weekly tutorials. The assessment consists of tutorial activities (10%), a project (20%), a mid-semester exam (20%) and an end of semester exam (50%). In 2010, the project consisted of writing up a research proposal for a Phase 3 clinical trial looking at the effectiveness of an emerging medication for a novel clinical indication. The proposals consisted of a number of sections including a project title, aims and background, significance and innovation, methodology, expected outcomes and a project budget.

INTEGRATING THE *ISLAND*

In 2011, the *Island* was integrated into the teaching (tutorials) and learning (projects) of the existing clinical trial course. The *Island* was used to deliver seven *Island*-based tutorials that demonstrated, applied, reinforced and assessed concepts covered in lectures. The following is a brief description of each tutorial.

TUTORIALS

In Tutorial 1, students were introduced to data collection using the *Island*. The logistics and issues of planning research was explored by having students complete a simple randomised controlled trial (RCT) using the *Island*. The RCT looked at the effect of alcohol on physical (heart rate, blood pressure, and 100m running time) and psychological (IQ and mental arithmetic) outcomes. The

concepts of statistical hypothesis testing, statistical power, selection bias, random sampling, and standard operating procedures were discussed while students gathered data for the RCT.

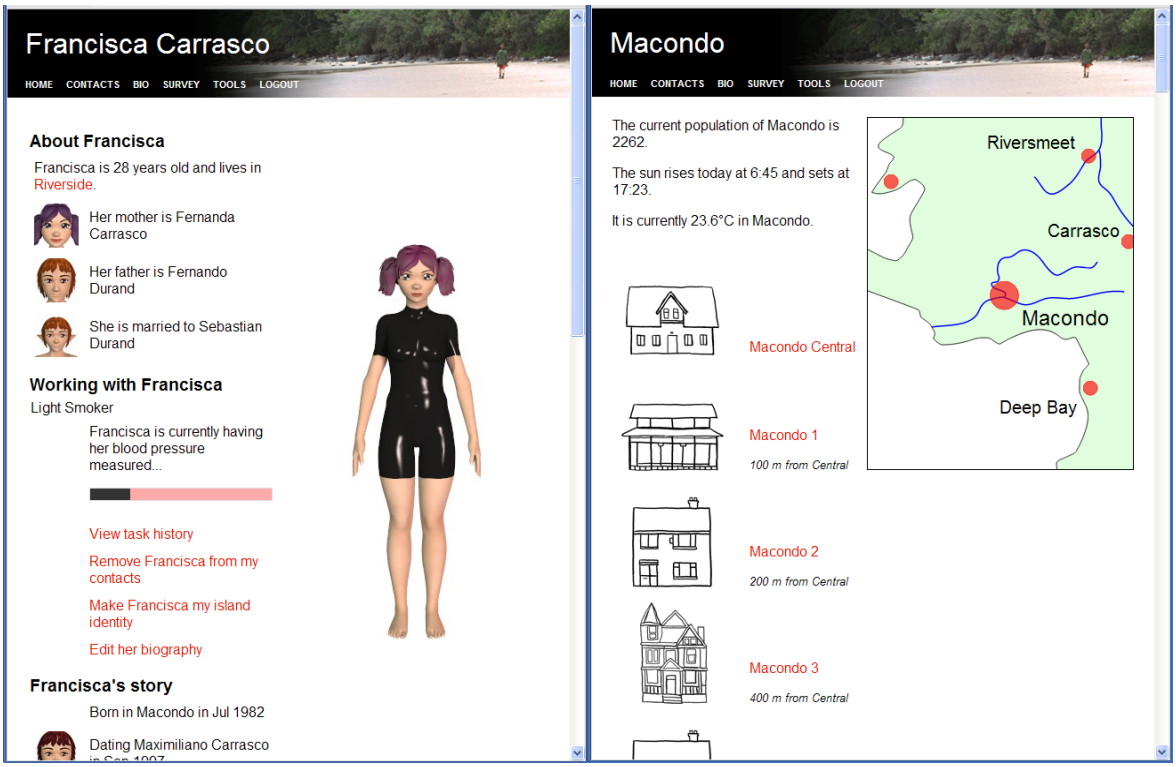

Figure 1: The *Island* web interface. To the left is an example of an Islander, named Francisca, having her blood pressure taken. To the right is an example of the district breakdown of the large city of Macondo. This geographic breakdown can be used to randomly select participants for clinical trials. However, they may refuse to consent.

Tutorial 2 covered further data collection, but with a focus on comparing and contrasting case-control and cohort epidemiology study designs. The students were required to design and conduct a case-control and cohort study looking at risk factors for common diseases on the *Island*. This allowed the differences of the two major research designs in epidemiology, in particular the influence of other variables, to be demonstrated to students. The concepts of statistical hypothesis testing, variability in data, selection bias and control groups were discussed with the study scenarios structured to demonstrate each concept.

Tutorial 3 demonstrated the difference between random sampling and random allocation by getting students to conduct a clinical trial looking at the effect of 10µg adrenaline vs. a placebo on pulse rate. Random sampling and random allocation was done with the aid of an online random number generator. The concept of random stratified sampling was also introduced.

Tutorial 4 was for biostatistics summative learning the *Island*. Experimental and epidemiology data gathered using the *Island* in Tutorials 1 and 2 were analysed in order to revise the concepts of statistical inference (hypothesis testing, *p*-values and confidence intervals). Students were also asked to repeat the RCT completed in Tutorial 1 using a larger sample. Each student was given a standard operating procedure for the experimental protocol. They were then required to randomly select, randomly allocate, and take two participants through the experimental protocol. All data from each student was submitted to the instructor and was used in Tutorial 5.

Tutorial 5 was further biostatistics summative learning for analysing an RCT. Data gathered at the end of Tutorial 4 looking at the effect of alcohol was analysed using SPSS. This tutorial focused specifically on comparing means using *t*-tests. The difference between independent samples and repeated measures was explored. The students also practiced reporting the results of their statistical analyses.

Tutorial 6 was an introduction to statistical power analysis and revision of the statistical analysis of experimental designs. Working in groups, students had to complete a simple pilot experiment either using a paired design or independent samples design looking at the effect of adrenaline on a physiological measure of their choosing. This pilot experiment was used to calculate an estimated effect size which was used to write up an *a priori* power analysis similar to what might be included in a research proposal.

Tutorial 7 covered the process of conducting a clinical audit to help illustrate Good Clinical Practice and demonstrate procedures completed after clinical trials. Students were required to bring in their project reports, project data, and completed case report forms. The students were taken through an example of an audit checklist by the instructor and were then required to complete the process on each other's projects. Each student played different roles in the clinical audit process by taking in turns being a clinical site monitor or a clinical research manager. This tutorial was designed to provide students both logistical and practical experience with conducting, and being the subject of a clinical site audit. It also provided a work relevant context for the understanding of critical regulatory requirements and good clinical practice in clinical trials, such as attribution, legibility, as well as contemporaneous, original and accurate recording of data.

PROJECT

The *Island* allowed us to expand the course project substantially from the 2010 project as the *Island* allowed students to conduct their own virtual clinical trials. For 2011, the project was split into three parts. Part I consisted of a research proposal outlining their planned clinical trial (5%). Part II consisted of a research report (10%) outlining the findings of the student's clinical trial written in line with the Consolidated Standards of Reporting Trials (CONSORT, Moher, et al., 2010). Part III composed of clinical auditor's reports integrated with the activities of Tutorial 7 (5%). Some examples of the diverse range of topics students choose included the effect of Dextroamphetamine on cognitive ability, Psilocybin-mushrooms for the treatment of depression, the safety of betel nut (Areca nut), the effect of Cannabis on intelligence, and the effectiveness of natural vs. synthetic insulin for the treatment of diabetes.

EVALUATION

In order to evaluate the effectiveness of integrating the *Island* into the clinical trial course, the first step was to evaluate students' attitudes towards using the *Island*. While this is an indirect method of establishing the effectiveness of the *Island*, surveys do serve an important initial step in validating the use of educational tools (e.g. Spinello & Fischbach, 2004). To do this, an *Island* questionnaire was administered to students enrolled in the clinical trials course during lab time in the final weeks of the semester. The questionnaire coincided with regular course evaluation surveys. Of the 32 students enrolled in the course, 29 (91%) responded. The mean age of the sample was 22 years (SD = 3) and was composed of 15 females and 12 males (2 respondents did not fill out demographic information).

The questionnaire consists of two parts, quantitative and qualitative. The quantitative part was made up of 18 items that aimed to measure three aspects of using the *Island*, *engagement*, *usability* and *contributes to understanding* (see Table 1). Each item was responded to on a seven point likert type scale ranging from (1) strongly disagree to (7) strongly agree. The proportion of respondents that agreed to each statement was also measured by counting the number of respondents who indicated slightly agree (5), agree (6) or strongly agree (7) to an item. Confirmatory factor analysis was not conducted due to a low 29:18 (1.6:1) subject to item ratio (Costello & Osborne, 2005) and therefore the validity of the proposed factor structure of the *Island* questionnaire remains to be confirmed. Reliability of each questionnaire domain was measured using the Cronbach's α coefficient of internal consistency which found that α =.89, .70 and .83 for *engagement*, *usability* and *contributes to understanding* respectively. Following the quantitative questionnaire, two open-ended questions were included for qualitative feedback. These questions were (1) "Share at least one positive experience of using the *Island*" and (2) "Was there anything that you did not like about using the *Island* or you think needs improvement?".

STUDENT PERCEPTIONS

Table 1, which shows the responses of the quantitative *Island* questionnaire, demonstrates a high degree of student engagement with the *Island* during the clinical trial course. Only a small proportion of respondents (6/28, 21.4%) expressed the attitude that that they did not enjoying using some aspects of the *Island*. Qualitative comments reported the Islanders' sleeping habits and the constant

repetitive clicking between pages as the main reasons for this feedback. Overall, 25/28 (86.2%) participants reported an overall positive experience and 28/29 (96.6%) enjoyed being in control of their own virtual experiment.

Table 1: Questionnaire Item Descriptive Statistics

Items*	*M*	*SD*	Agree	% Agree	*N*
Engagement (Cronbach's α = .89)					
Enjoyed using for project	5.69	1.56	25	86.2%	29
Enjoyed being in control of virtual study	5.90	0.72	28	96.6%	29
Did not enjoy using for projects	2.71	1.70	6	21.4%	28
Felt immersed in virtual study	4.82	1.22	19	67.9%	28
Recommend to other students	5.38	1.72	23	79.3%	29
Positive experience overall	5.75	1.14	25	89.3%	28
Ease of Use (Cronbach's α = .70)					
Easy to use	5.48	1.40	25	86.2%	29
Difficult to use	3.57	1.75	11	39.3%	28
Learning to use was difficult	2.14	1.03	2	6.9%	29
More instructions needed	3.41	1.78	12	41.4%	29
Easy to conduct virtual scientific studies	5.45	1.21	25	86.2%	29
Contributes to Understanding (Cronbach's α = .83)					
Better understanding of scientific research design	5.46	1.07	25	89.3%	28
Appreciation for practical consideration of scientific research	5.79	0.98	27	93.1%	29
Improved understanding of how data is collected	5.28	1.03	25	86.2%	29
Better understanding of statistical analysis in scientific research design	4.96	1.20	22	78.6%	28
Improved confidence with design, implementation and analysis of scientific studies	5.72	0.92	27	93.1%	29
Experience with statistical issues that arise during research	5.45	1.06	24	82.8%	29
Improved understanding of how scientific studies are analysed	5.21	1.18	21	72.4%	29

Note. *Items have been condensed. *M* = Mean, *SD* = Standard deviation, Agree = the number of participants who agreed (scored 5, 6, or 7) to an item, *N* = number of responders to item.

The most common complaint in relation to the *Island* was difficulty integrating the *Island* into the student's existing late night study habits. These students discovered that, just like themselves, the Islanders have unpredictable sleeping habits. Students felt that this was a disadvantage. One student explained, "*The fact that the Islanders sleep is difficult for the uni student. Some students may work quite a bit and are not able to perform tests at normal times*". Similar feedback was reported by Bulmer (2010).

According to the qualitative feedback, high engagement with the *Island* could be attributed to the realism and interactive nature of the *Island*. For example one student stated, "*It feels like they're real people*". Students also felt engaged during tutorials where the *Island* was utilised. One student stated, "*I like how the learning experience is so interactive*". Without the *Island*, the practical and ethical limitations imposed on clinical trial research would have impacted on the ability to actively engage students in learning about clinical trials. In terms of improvements, some students requested a more diverse range of tasks to be available to experiment with.

The *Island* was reported to be relatively easy to learn and use, although 12/29 (41.4%) participants agreed that more instructions would be welcome. In terms of conducting virtual experiments, 25/29 (86.2%) agreed that the *Island* made it relatively easy to do. There appeared to be a discrepancy between the items "easy to use" and "difficult to use" with 25/29 (86.2%) and 11/28 (39.3%) participants agreeing with each item respectively. This inconsistency probably reflects the perceptions that while the *Island* was overall easy to use (e.g. finding participants for trials), there were still elements that remained difficult (e.g. too much clicking between pages).

In terms of the *Island* contributing to the students' understanding of the design, management and analysis of clinical trials, there was an overall high level of agreement (see Table 1). Feedback from one student stated "*In my opinion, using the Island can help me get a better understanding of clinical trial studies*". Use of the *Island* seemed to particularly excel at giving students a better understanding

of the practical considerations of clinical trials (27/29, 93.1%) and improving their confidence with the design, implementation and analysis of clinical trials (27/29, 93.1%). For example, one student reported in the qualitative comments that "[the *Island*] *gave you a more appropriate appreciation to how trials work and are made*". The lowest level of agreement was for the statistical analysis of clinical trials with 21/29 (72.4%) students agreeing that the *Island* improved their understanding. This can be attributed to the orientation of the course being more so towards the design and management of clinical trials and not statistical analysis.

DISCUSSION AND CONCLUSIONS

The integration of the *Island* into a clinical trial course allowed an unprecedented ability to overcome the universities limitations of providing authentic and work relevant learning experiences for pharmaceutical science students. The *Island* achieved this by simulating a virtual environment where students were able to design, conduct, analyse, and report the results of their own virtual clinical trials. The *Island* was embedded within tutorials which aimed to demonstrate, apply, reinforce and assess clinical trial concepts covered in lectures, and it was also utilised for projects to provide students with experience in independently conducting their own virtual clinical trials. Student evaluations of this integration were highly positive. Students reported feeling engaged in their own virtual experiments, at ease with using the Island for their coursework and noticed improvements in their understanding of clinical trials. According to the qualitative comments of the students, the *Island's* success lies in its realism and ability to get students actively involved in their learning.

It is also necessary to note the limitations to using the *Island*. The Islanders' sleeping habits were the most common student grievance. Many students believed that the Islanders should have a "wake up" button. We believe that such a feature leads to an important lesson for students regarding scientific research. Scientists must organise their studies around the lives of their participants, not vice versa. Regardless, busy students who have to juggle work and study commitments may have no other option but to complete their clinical trials while the Islanders sleep. The Islanders' sleeping habits remains the most controversial design element of the *Island* (Bulmer, 2010).

From our perspective, the integration of the *Island* was a pedagogical boon. For the first time in our clinical trial course, we were able to get students experiencing what we were teaching. Students were able to learn through their experiences of designing virtual clinical trials, controlling variables, using placebos, randomly sampling participants, randomly allocating participants, statistically analysing results, and, for the first time, conducting clinical audits. This was all achieved within the constraints of a regular university course. While there were a number of technical issues with the Island and the computer technology required to access to the Island in tutorials, these issues are endemic with all educational technology and not an issue specific to the *Island*.

In conclusion, for courses that require students to experience and develop relevant and work-related skills within the significant constraints of tertiary education (e.g. time, resources, ethics), online virtual simulation tools may be a viable teaching and learning tool. In this study, integrating the *Island* into the teaching and learning of a course in the design and management of clinical trials was successful from both the students' and instructor's perspective. In fact, we cannot envisage delivering future courses without the aid of the *Island*. However, this conclusion is based on attitudinal outcomes. Future research is needed to compare the benefits of using the *Island* on academic outcomes related to clinical trial design and management course outcomes.

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