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EDITORIAL

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EUROTHERM3235Trial

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There are many reasons for performing clinical trials, the most important being to gain new knowledge that can be incorporated into clinical practice and improve patient outcome. However, there are other important secondary benefits, including an observation that the design of trials is connected to the social order of medicine [1, 2]. This social order or professional standing is important for our speciality.

In 2008 the EUROTHERM3235Trial was announced at the general assembly of the European Society of Intensive Care Medicine (ESICM). The trial was the result of a Delphi exercise surveying ESICM members' views. The EUROTHERM3235Trial emerged, was supported (http://www.eurotherm3235trial.eu) and started in January 2009 with protocol development [3].

The EUROTHERM3235Trial (http://www.eurotherm3235trial.eu) is the most important clinical trial in critical care medicine ever conceived by European intensive care medicine because it was launched and funded by the ESICM and will be the largest non-commercial, randomised controlled trial ever conducted in Europe due to the substantial number of centres that are required to deliver the target number of patients (1,800). This is a new and fundamental step for intensive care medicine in Europe.

The burden of bureaucracy that investigators now have to face to conduct clinical trials is larger than ever before, and this inevitably causes a slower than expected start of recruitment and initiation of new countries and centres [4, 5]. These challenges included the EUROTHERM3235Trial database, which presented a number of contracting and development issues but now has the appropriate functionality for a randomised controlled trial. The contract was signed on 10/11/09, but legislative impediments [Commission Nationale De L'informatique Et Des Libertés (CNIL)] have meant that the data server(s) are now hosted at the University of Edinburgh (UoE). *CYIM* (Intellegence Informatique du Monde Scientifique, http://www.cyim.com/), which hosts the trial website and provides a password-protected hyperlink to the database, was necessarily involved in this setup phase. The database went live on April 9, 2010, and prior to this, the trial could not randomise patients outside of Edinburgh.

Detailed contracting is now necessary for all clinical trials. The contracts drawn up for the Eurotherm3235Trial include: (1) the financial contract between ESICM and UoE; (2) the provision of the trial database by Lincoln, ESICM and UoE; (3) clinical site agreements between UoE and each recruiting centre (necessary since we are paying a per-patient payment); (4) separate contracts for the UK and international sites including Italy, Germany, Russia, Hungary and Greece were required to incorporate

the laws of each participating country. International contracts have been translated to a legal standard then similarly back-translated to ensure consistency, and this takes approximately 6 weeks; (5) a service level agreement has been drawn up between the Chief Investigator and the UoE for the data stored in Edinburgh. Many of these processes were conducted for the first time (as part of a large RCT) by ESICM.

Nevertheless, this trial has already achieved many important milestones. The trial is registered with the European registry of trials (http://www.controlledtrials.com ISRCTN ISRCTN34555414). Sponsorship has been agreed upon: the trial is co-sponsored by the UoE and NHS Lothian in the UK and the UoE outside the UK. Insurance for non-negligent harm has been provided by the University of Edinburgh for European and Australasian centres, but the associated high per-claim-deductable for USA centres has slowed progress in North America. Research ethics committee (REC) approval was obtained in Scotland and England in June 2009 and Hungary, Eire, Estonia, Russia, Italy and Germany in May–July 2010, and there are well-advanced submissions in Greece, Portugal and Belgium. Local administrative approval has been obtained in eight sites throughout the UK, site contracts have been signed for eight UK centres, two Greek and one Italian centre to date. National Institutes for Health Research (NIHR) Portfolio Adoption was achieved following a complex and time-consuming process in the UK. This does however make the trial more attractive to UK centres.

In clinical trials, it is expected that the first patient randomised will take 1 year from initiation and, in the case of Eurotherm, that is from January 2009. The first patient was recruited in November 2009, and current recruitment can be seen by visiting the trial website. Trial documentation has been translated into various European languages including Italian, French, German, Dutch, Estonian, Russian, Hungarian, Greek, Flemish and Portuguese.

Such a large trial requires enormous coordination and monitoring effort. For this reason, trial committees have been appointed and include:

(1) Independent "Trial Steering Committee". The first meeting occurred in March 2010.
(2) Independent "Data and Safety Monitoring Committee" (DSMB). The Chairman is Prof. Peter Suter, who was appointed by the ESICM. The DSMC Charter was approved by DSMC members in accordance with the DAMOCLES project [6, 7], and their first meeting was in February 2010.
(3) The International Advisory Board, who helped to develop the trial protocol and will provide expertise during this trial.
(4) Trial Management Committee who deal with the day to day running of the trial.
(5) Research, Scientific and Finance committee, appointed by the ESICM and chaired by Prof. Charles Sprung, to provide a fiduciary vigilance for the trial.

An online eCRF and randomisation service was made available from 9 April 2010, and training is currently being extended to all centres able to recruit patients. At the time of writing, another 30 centres are being progressed internationally (ethics submitted), and there are up to 193 ICUs who have expressed an interest in the trial by returning a centre survey (available from the website). Current emphasis has been upon establishing the recruitment infrastructure, which is ongoing. This effort required an extremely high level of input; however, we are glad to say that the trial is in good shape for the challenge ahead, the recruitment phase of the EUROTHERM3235Trial.

The EUROTHERM3235Trial will answer an important scientific question that will hopefully improve patient care. It will also and importantly establish Intensive Care Medicine in Europe as a mature and identifiable specialty, and perhaps increase ICM's social order within medicine. The trial is open to all ICUs, and we encourage you to visit the trial website, register an interest and complete a centre survey. The trial staff are available to help you with regulatory submissions. This trial is logistically challenging due to the large number of centres required, and at present the trials office has an emphasis on building recruitment capacity. We need all of your help to make this study a success and thank those investigators for all their work to date.

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