Cambridge University Hospitals NHS
NHS Foundation Trust

July 2014

CCTU

15th Edition

Cambridge Clinical Trials Unit Bulletin

The DILT1D study:

Academic led, single center clinical trial completed ahead of schedule

The A**d**aptive study of **IL**-2 dose on regulatory T cells in **t**ype **1** **d**iabetes (DILT1D) trial has recently been successfully completed eleven months ahead of schedule. The trial initiation was held on March 22nd 2013 and LPLV was completed on 15th May 2014. The study protocol was intensive, requiring eleven visits over 9 weeks: a screening visit, treatment visit, daily visits for the 4 days, twice weekly visits for the second week, weekly for week three and four followed by final visit on week 9[1]. In total 45 participants with recently diagnosed type 1 diabetes were screened and 40 met the inclusion criteria and were treated with a single dose of aldesleukin (IL-2). A total of 735 patients were identified as potential participants. Direct communication was made with 317 of those individuals by the study team. Participants for the study were identified using three main sources: type 1 diabetes disease registers (19%); clinics (26%), or via the most successful method, self-referral through the study's website (54%) http://www.clinical-trials-type1-diabetes.com and social networking sites e.g. Facebook/ClinicalTrialsType1Diabetes & Twitter (@t1diabetestrial).

Peaks in website activity and website referrals corresponded with targeted publicity events demonstrating that successful recruitment is dependent on active and targeted publicity to achieve patient engagement. Website referrals increased the geographical spread of recruitment leading to the international accrual of participants from Ireland and France. Distance to the NIHR Cambridge Biomedical Research Centre, Addenbrooke's Hospital was not an obstacle to recruitment. Study visits were performed at either the NIHR/Wellcome Trust Clinical Research Facility or in the home or workplace to increase flexibility and to facilitate participation in the study.

The Chief Investigator**, Dr Frank Waldron-Lynch** from the JDRF/Wellcome Trust Diabetes and Inflammation Laboratory, Cambridge Institute for Medical Research was supported by the Cambridge Clinical Trials Unit (CCTU) who provided co-ordination, data management and statistical input for the study.

As a result of the success of DILT1D, funding has been secured for the next study from The Sir Jules Thorn Charitable Trust which will determine the frequency of aldesleukin administration required to maintain increased Treg function. This trial is planned to start in Q3 2014.

1. Waldron-Lynch F, Kareclas P, Irons K, et al. Rationale and study design of the Adaptive study of IL-2 dose on regulatory T cells in type 1 diabetes (DILT1D): a non-randomised, open label, adaptive dose findingtrial. BMJ Open 2014;4:e005559.

The SIEGE of Pancreatic Cancer

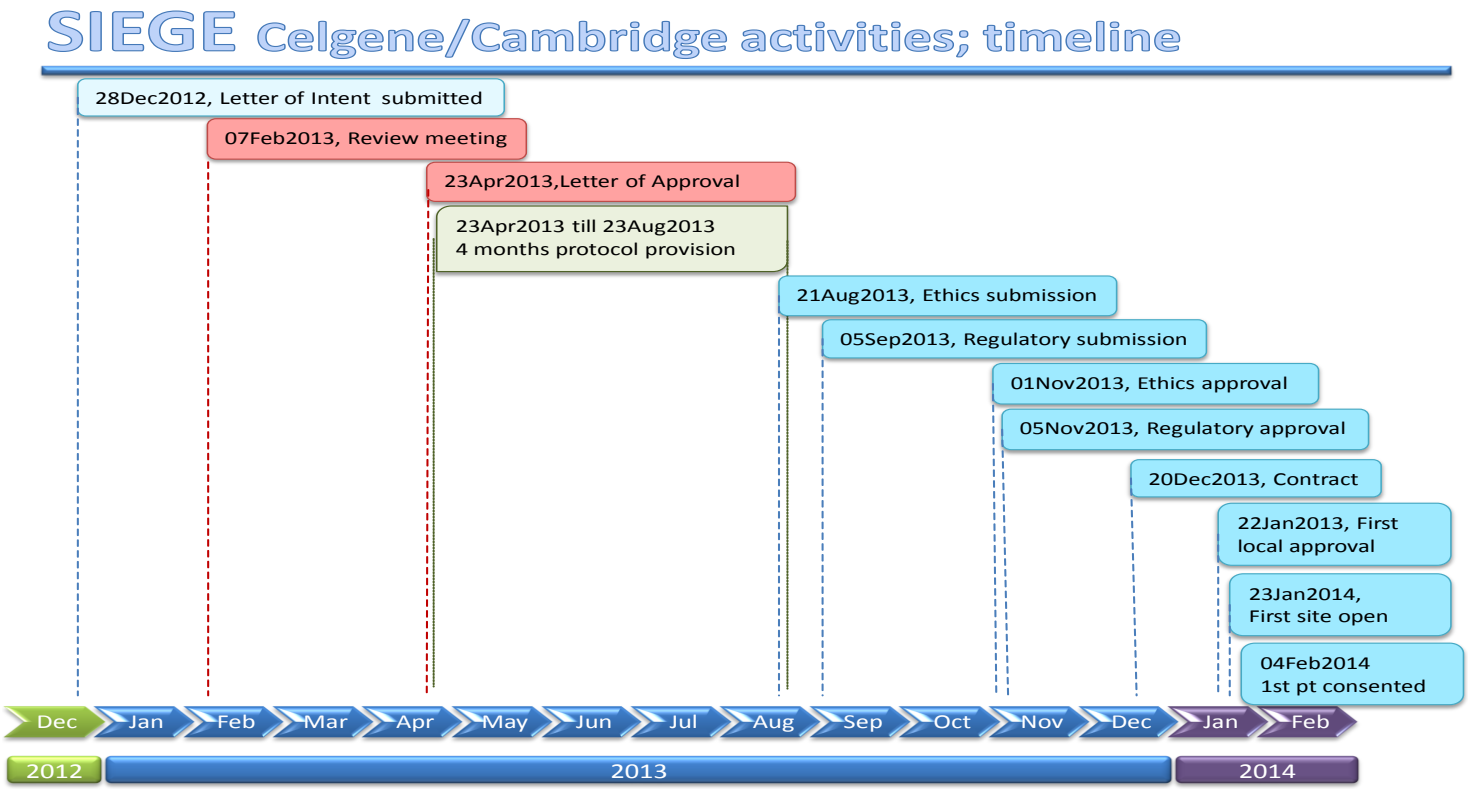
Pancreatic ductal adenocarcinoma (PDAC) is responsible for 32,500 deaths per year in Europe. Mortality rates match incidence rates and most patients present with inoperable disease, with median life expectancy under 1 year despite intervention. These sobering statistics highlight a great need to improve treatment options for PDAC.

Until recently, gemcitabine (GEM) was the only chemotherapy drug licensed for use to treat advanced PDAC, offering only modest survival gains. Recently, an international phase III trial conducted outside of the UK confirmed that Abraxane (ABX) combined with GEM improved survival compared with GEM alone (Von Hoff *et al*, NEJM 2013). The mechanism by which ABX interacts with GEM to improve anti-tumour activity is not clear; however preclinical studies undertaken in the CRUK-Cambridge Institute suggested that giving ABX 24 hours prior to GEM might result in higher intra-tumoural GEM concentrations. Thus, scheduling of the two drugs may be critical to optimising clinical benefit.

Dr Pippa Corrie (Consultant and Associate Lecturer in Medical Oncology) recently opened SIEGE: an investigator-led, CUH-sponsored multicentre, NIHR portfolio randomized phase II trial to investigate two different schedules of ABX combined with GEM as first line treatment for metastatic PDAC. The primary end point of SIEGE compares the outcome of concomitant (same day) or sequential (24hr delay) administration of ABX combined with GEM in terms of progression free survival. Other key endpoints include quality of life, health economics and biological analyses of patient samples to explore mechanism of action of the combination regimen

The trial boasts an impressive set up time (Figure 1): from receipt of a grant approval letter issued by Celgene (ABX manufacturer) in April 2013, the trial took just over 9 months to first patient consented. This outstanding achievement is the result of close collaboration between Celgene, CCTU and the various elements of the Cambridge Cancer Centre: CCTC, Oncology Department and CRUK-CI.

To date, 7 of 20 proposed sites are open to recruitment, 10 patients have been randomized and the trial is on target to recruit a total of 120 patients within 18 months.



IIVoP study is now open for recruitment!

Clinical Trial of Ivabradine on Capsaicin-Induced hyperalgesia in Healthy Volunteers

Neuropathic pain can occur when nerves are damaged, for example in diabetes, during shingles or after trauma from an accident or surgery. Such pain is very persistent and is very difficult to manage. Patients often report that currently available medication for neuropathic pain are ineffective or have intolerable adverse effects.

IIVoP builds on seminal research led by **Professor Peter McNaughton** in the Department of Pharmacology in University of Cambridge. His group revealed that HCN-2 channels are critical for the development of pain after a nerve injury. They found that mice that had these HCN-2 channels genetically deleted from nociceptors or 'pain-causing' nerves did not have pain after nerve injury. Hence, drugs that block HCN-2 channels could be useful for treating neuropathic or nerve-injury pain.

Ivabradine, a non-specific HCN blocker, is currently licensed for the treatment of angina in patients. IIVoP would investigate the effects of Ivabradine on increased pain sensitivity (hyperalgesia) that is induced by capsaicin in healthy volunteers. Capsaicin is the active ingredient of the chilli pepper. A small amount of capsaicin cream would be applied temporarily to the forearm to sensitise the skin to standardized heat and mechanical stimulation. This mimics the increased skin sensitivity that is reported by patients with chronic neuropathic pain. IIVoP would ascertain whether Ivabradine reduces the capsaicin-induced pain sensitivity. If that is the case, Ivabradine and other more specific HCN blockers may be worth developing as an entirely new class of medication for the treatment of neuropathic pain in patients.

IIVoP is a randomized, double blind, placebo-controlled clinical trial that aims to recruit 24 healthy volunteers. The safety of Ivabradine is well established in healthy volunteers who would only be enrolled on the drug trial if they show sensitivity to capsaicin cream during screening.

The Chief Investigator of the study is **Dr Michael Lee** from the Division of Anaesthesia in the University of Cambridge. The Cambridge Clinical Trials Unit (CCTU) is providing co-ordination, data management and statistical input for the study. The UK Medical Research Council and the Cambridge Biomedical Research Centre are funding the trial.

IIVoP opened at Addenbrooke's Hospital on 02 July 2014 and is now actively looking for volunteers to take part. For further details and to register interest as a participant, please contact Dr Michael Lee and team on 01233 217888, or email pain@wbic.cam.ac.uk. Participants should be aged between 18-64, completely healthy without any pain and not on any medication. We are looking forward to hearing from you.

Important changes to CUH biochemistry reference ranges - 01 July 2014

From 01 July 2014 CUH will be altering some of our reference ranges, where applicable, to comply with the DOH-supported initiative to harmonise reference intervals or to reflect the reference ranges recommended by the suppliers of our instrumentation. The absolute values reported will not change significantly except for those drugs (carbamazepine, digoxin, phenobarbitone, phenytoin and theophylline) where we have changed to mass units.
Visit the clinical biochemistry and immunology pages on CUH-Connect for more information or call the duty biochemist if you have any queries on ext 3151.

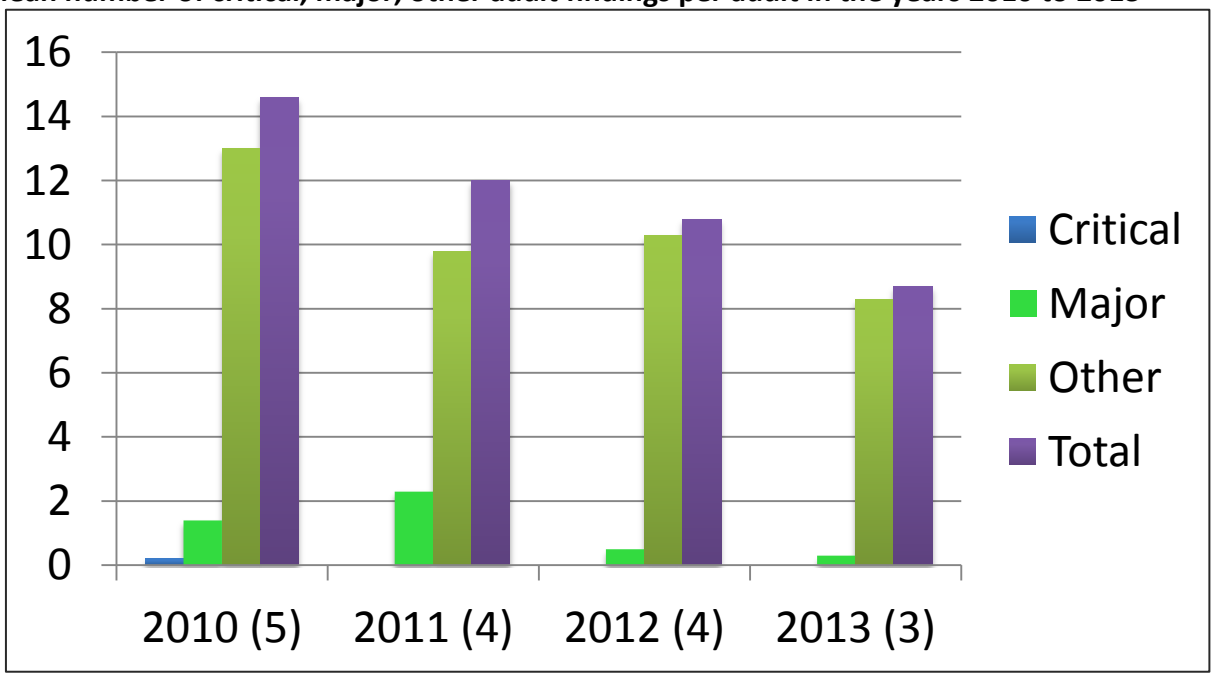
Note to trial coordinators: up-date your files with the new reference ranges now!

Quality Assurance: Impact of routine Audit Programme

Cambridge University Hospitals NHS Foundation Trust (CUH), as a Sponsor of CTIMPs maintains an Audit Programme conducted by an independent auditor. Recently, the auditor (Shirley Hallam) reported in a very detailed talk the audit strategy, audit findings and trends to the academic clinical trials teams. She compared the audit findings per audit over the last 4 years (2010 to 2013) and it is evident that there is a clear trend of decreasing numbers of findings per audit, as well as a trend to less sever findings, meaning that overall the quality of the trials has improved.

This is a clear indication that the ongoing monitoring and quality control by the Regulatory Team, as well as training and clear standard operation procedures improve the quality of trial conduct, GCP compliance and data accuracy.

Mean number of critical, major, other audit findings per audit in the years 2010 to 2013



CCTU grant applications review 2012/13 - 50% success rate!

Since January 2012 the CCTU has been involved in working with investigators on a total of 88 grant applications. 15 were withdrawn after submission by investigators; 20 never reached submission stage; but of the 55 submitted applications, 28 were successful.

This is a success rate of just over 50%. Congratulations to all involved!

Critical Findings:

TMF filing and corrective actions in the spot- light

The recently published definition of what constitutes a critical finding in an MHRA GCP inspection makes it clear that incomplete and badly maintained TMFs, as well as insufficient or untimely corrective actions to manage previous major findings are grounds for giving a critical finding.

Going forward, this means if a TMF is not readily available or accessible, or the TMF is incomplete to such an extent that it cannot form the basis of inspection and therefore impedes or obstructs inspectors carrying out their duties in verifying compliance with the Regulations, constitutes a critical finding.

Therefore, a reminder to all trail teams and investigators: Please keep your TMF in order at all times and deal with any necessary corrective (and preventive) actions to the given deadlines and as specified and recorded.

Mandatory posting of clinical trial summary results on the European Clinical Trials Database

As of 21 July 2014, it will become mandatory for all CTIMPs to post clinical trial results in the European Clinical trials Database (EudraCT), managed by the European Medicines Agency (EMA). These summary results of clinical trials will then become available to the public.

What this means for CUH chief investigators conducting CUH sponsored CTIMPs?

We will now be obliged to post results in EudraCT for any interventional trial registered in EudraCT that have ended within a certain period of time. In short, it will affect all current, past and future EudraCT registered CTIMPs.

For any CTIMPs that ended on or after 21 July 2014, we will have to post results within six or twelve months following the end of the trial, depending on the type of trial concerned, and for trials that ended before that date, we also will need to submit the results retrospectively.

The CCTU regulatory Team will provide guidance and timelines individually to Chief Investigators of CUH sponsored CTIMPs in due course.

Book mark: MHRA website changes

MHRA website will soon be moving to GOV.UK. To find out the latest information on how this will affect you, please read the Moving to GOV.UK page on the current MHRA website.

Up-date on the new EU Regulation on Clinical Trials

The new EU Regulation on Clinical Trials on Medicinal Products for Human Use (EU No. 536/2014) was published in the Official Journal of the European Union on **27 May 2014** and will come into force on the **16 June 2014.**

What does this mean for us?
Before the new regulation is applied across all the Member States, the necessary EU Portal and EU database need to be fully functional and meet the functional specification. It is only once this is in place that a notice will be published of the timelines for full implementation across the EU start. This means so far there is no date set. However, it is anticipated that this will be in **November 2015.**

What happens now?
All trials which have submitted a request for authorisation before **28 May 2017 or within 18 months of the publication** (whichever the latter), the trial may continue to be started and conducted under the current EU Directive/UK Statutory Instrument legislation until **28 May 2019 or 42 months after the publication**(whichever the longer).

Important for your CTIMP timeline planning: This means that any trial ongoing after this date will need to transfer to the new EU Regulation and comply with all the requirements.

However, please keep in mind that MHRA, REC and Sponsor requirements may change at differing time points in order to ensure that they are able to comply with the new regulations when they are officially fully implemented.

What to do?
CCTU regulatory team will keep you informed at all times of any new information. Watch this space!

CCTU SOP up-date

Following the statutory, routine GCP inspection by the MHRA, the corrective and preventive action plan made it necessary to up-date our SOPs and related documents, as well as the development of new SOPs.

Updated documents:
CCTU/FRM003 Pregnancy Reporting Form
CCTU/FRM010 Monitoring Log
CCTU/FRM062 Registration of Interest/Request for Study Protocol
CCTU/FRM065 Remote Monitoring Report
CCTU/GD027 CCTU ReDA User Guide
CCTU/SOP003 DSUR& Annual Progress Reporting
CCTU/SOP004 End of Trial Procedures (CTIMPs)
CCTU/SOP012 Management of Controlled Documents
CCTU/SOP013 Paper Case Report Form Design
CCTU/SOP014 Amendment Management of CTIMPs by Teams
CCTU/SOP018 Handling Protocol or Regulatory Non Compliance
CCTU/SOP033 Database Locking
CCTU/SOP038 MACRO Database Security
CCTU/SOP040 Risk Assessment Process for CTIMP's
CCTU/SOP044 Research Sample Management
CCTU/SOP047 CTIMP Start up Procedure for Trial Teams
CCTU/TPL001 Protocol Template
CCTU/TPL002 Patient Information and Consent Template
CCTU/TPL009 Trial Specific Data Management Plan

New Documents:
CCTU/FRM086 Participating Site initiation Form
CCTU/GD029 CTIMP Submission Documents
CCTU/POL001 Quality Policy
CCTU/SOP024 Initiation Meeting for CTIMPs
CCTU/TPL028 Participating Site Activation Letter
CCTU/TPL029 Trial Initiation Agenda
CCTU/TPL030 Monitoring plan
CCTU/TPL031 Sample Tracking and Processing Template

Documents can be found on our Resource pages at http://www.cuh.org.uk/cms/research-and-development/clinical-trials/cambridge-clinical-trials-unit/resources/standard-operating

New Surgical and Peri-operative Care Theme (SPeC)

CCTU Surgery and Peri-operative Care Theme

In response to the growing interest in trials for surgical patients, the CCTU have recently established a new theme, namely the Surgical and Peri-operative Care theme (SPeC).

Professor Peter Hutchinson, Professor of Neurosurgery, University of Cambridge, heads this theme and Carole Turner, who is the Research Development and Clinical Trials Manager for the Society of British Neurological Surgeons, has been appointed as the SPeC theme representative on an operational level.

Professor Hutchinson has recently been appointed as the Neurosurgical lead for the Clinical Trials Initiative of the Royal College of Surgeons of England. Along with Angelos Kolias, chair of the British Neurosurgical Trainee Research Collaborative (BNTRC) and Neurosurgical lead for the IDEAL Collaboration, hopefully we can bring the two themes in line and provide the support to develop new surgical trials and surgical CIs/PIs.

Please do contact us if you wish to discuss any potential new proposals.
Peter Hutchinson pjah2@cam.ac.uk, Carole Turner clt29@medschl.cam.ac.uk, Angelos Kolias ak721@cam.ac.uk

Peter Hutchinson

Carole Turner

Angelos Kolias

The Cambridge Strollers raised nearly £3500 for ACT-Cancer & Teenage Cancer Trust. Thanks to all who donated. Carolyn, Richard & Claire went the full distance of 100k of the Grand Union Canal challenge. Kevin, Sandra and Cathy still managed more than half. Congratulations to them! Donations still welcome!

CCTU Staff News

Congratulations to **Biljana Brezina**, who has completed her executive master's course in Clinical Trial Management at Cranfield University in May 2014. She graduated with distinction, and won the prize for best student in class.

The formal taught component of this course comprises eight modules (each module is delivered over three days at Cranfield University), Core Principles Integration - Integrating Portfolio and an Individual Research Project. The research project was undertaken at Biljana's place of work in the Vasculitis Clinical Research Group, benefitting her, the Vasculitis Team and patients with Vasculitis.

Her research project was entitled "Infection complicating cyclophosphamide treatment in anti-neutrophil cytoplasmic antibody (ANCA) - associated vasculitis". In this study, the relationship between the cumulative cyclophosphamide dose and occurrence of infection was explored, which validated the current approaches to dosing and reductions for age and renal function. Completing this while working full time and looking after a young family is a great achievement, made possible with the support and guidance from the Head of the Vasculitis Research Group, Dr. David Jayne, providing mentorship and guidance throughout.

Dr Emma Arbon, a Biomedical Sciences, with a MSc in Toxicology from the University of Surrey, worked as a Clinical Trials Officer collecting and analysing data at the Surrey Clinical Research Centre, a Phase I supplementary accredited research unit conducting commercially sponsored phase I-IV clinical trials and academically funded trials.

In 2009, Emma began her PhD studies in sleep-wake regulation at the Surrey Sleep Research Centre, University of Surrey, focusing on quantitative analysis of the EEG in human sleep, included pharmacological manipulation of sleep, sleep deprivation, and inter individual differences in sleep-wake regulation. In 2014, Emma received her PhD with a thesis titled "The EEG as a biomarker for individual differences in the pharmacology and physiology of sleep-wake regulation".

Emma was delighted to join the Cambridge Clinical Trials Unit in June this year as a Clinical Trials Coordinator, keen to learn new skills and to develop existing ones as she embarks on a new chapter in her career

Louise Grierson joined the CCTU Data Management team at the end of May as a Clinical Trials Data Manager from Exp-e-Data (UK) Ltd and brings her Data Management experience from working in the Pharmaceutical Industry for many years. Louise is based in the CCTU office in the Clinical School and is working on the Ritazarem trial. She is looking forward to making a contribution to CCTU and to furthering her data management skills within a research environment.

Congratulations to **Andrea Cradduck** and **Sarah Cheung** on becoming Senior Clinical Trials Monitors.

CCTU also welcomes **Andrea Machin** (Statistician), and **Louizos-Alexandros Louizos** (Programmer) to the Cambridge Clinical Trials Unit.

Kathryn Irons is going on maternity leave by end of July. All of us at CCTU are wishing her and the baby all the best.

Cambridge Clinical Trials Unit

General Enquiries to CCTU
cctu@addenbrookes.nhs.uk

SAE Submissions to CCTU
cctu@addenbrookes.nhs.uk
Fax: 01223 256623
General Fax: 01223 256763

CCTU | Website: www.cuh.org.uk/cctu

NIHR Good Clinical Practice (GCP) courses held on the Addenbrooke's site during 2014:

Introduction to Good Clinical Practice (GCP) – full day
Thursday 17/07/2014
Wednesday 22/10/2014
Thursday 11/12/2014

Good Clinical Practice (GCP) Refresher – 3 hours (for researcher's who have had previous GCP training)
Monday 21/07/2014
Tuesday 28/10/2014
Monday 15/12/2014

Advice on how to register for a LMS account or book onto a workshop can be found on the NIHR CRN website . The course can only be booked via http://www.crn.nihr.ac.uk/learning-development/booking-on-to-a-course/.

If you have any questions, please don't hesitate to contact myself or Beverley Reynolds beverley.reynolds@addenbrookes.nhs.uk for further information.

GCP Training – 2014

September 2014

Full GCP Session	Monday	22nd	am	08.30	12.30	ATC 6B
GCP Refresher	Monday	22nd	pm	13.00	15.15	ATC 6B
Full GCP session	Tuesday	23rd	am	08.30	12.30	ATC 3

November 2014

Full GCP session	Monday	24th	am	08.30	12.30	CS Seminar room 2
GCP Refresher	Monday	24th	pm	13.00	15.15	CS Seminar room 2
Full GCP Session	Tuesday	25th	am	08.30	12.30	CS Seminar room 2

For further details, please contact - Sylvie Robinson (Ex 58490) sylvie.robinson@addenbrookes.nhs.uk

Cambridge Clinical Trials Unit Contacts

Feedback or suggestions please email us at cctu@addenbrookes.nhs.uk
For the full list of contacts please see the contacts page on the CCTU Website.

SAE Submissions to CCTU	**cctu@addenbrookes.nhs.uk**	**Fax:** 01223 256623	**General Fax:** 01223 256763

CCTU | Website: www.cuh.org.uk/cctu

Cambridge Clinical Trials Unit | Box 401 | Coton House Level 6 | Cambridge University Hospitals NHS Foundation Trust | Addenbrooke's Hospital | Hills Road | Cambridge | CB2 0QQ