DOCTOR OF MEDICINE

Photoallergic contact dermatitis in Europe

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7. Conducting the EMCPPTS

The findings presented in Chapter 6 demonstrate that it was possible to conduct a large, prospective, multi-centre clinical study. This Chapter describes the different steps needed to allow this venture to progress and gives an overview of the many problems that were encountered. By doing so, it is hoped that some of the lessons learned could be applied in order that future studies can be undertaken to allow PPT series to remain clinically relevant.

A summary of the significant events and delays detailed is depicted in Figure 7.1 near the end of the Chapter.

7.1 Why perform the EMCPPTS?

As alluded to in previous Chapters, photoallergy and PPT testing had historically been somewhat of a "Cinderella" specialty, falling between the expertise of clinicians from contact dermatitis units and photobiology units. The prospective UK PPT study of Bryden *et al* which recruited subjects between 2000 and 2002 was a significant step towards increasing the level of knowledge about the relative frequency of PACD to several common photoallergens.[1] It also promoted PPT as an investigation when using the newly agreed European consensus PPT methodology.[2] It was therefore imperative to build on the foundation of the UK study by conducting a Europe-wide study using a similar methodology in a larger amount of centres. Aside from its wider geographical coverage, the EMCPPTS was to incorporate testing to more of the "newer" organic UV absorbers and topical NSAIDs, which were not included in the UK study.

7.2 The EMCPPTS initiation meeting

In February 2007 a one day meeting was held in Amsterdam, The Netherlands to discuss setting up the EMCPPTS. It was held under the auspices of the ESPD and the ESCD and funded by the ESCD and departmental funds from the Photobiology Unit in Dundee. The invited delegates were leading experts in the field of photoallergy and PPT from across Europe and comprised contact allergy clinicians, photodermatologists and photobiological scientists. A draft study protocol had been produced and taken by the Dundee delegates to aid and stimulate discussion. After discussion at the meeting, the following consensus points were agreed:

- It was intended that the EMCPPTS would commence on the 1st of January 2008. Initially some delegates had suggested the 1st of August 2007 but the other delegates felt this was too early to allow adequate preparation.
- The countries that would potentially participate were as follows: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Holland, Hungary, Ireland, Italy, Poland, Portugal, Spain, Sweden, Switzerland, and the UK. The draft protocol was to be refined before being sent to potential PIs in these countries who may be interested in joining the study.
- There would be a target minimum of 1,000 patients recruited. If this had not been achieved after one year, the study would continue in order to recruit more patients.
- Only PIs in centres that felt they could PPT $\geq$ 20 patients per year would be invited to participate.
- Standard fluorescent PUVA lamps were to be used for irradiation.

- UVA dosage meters from each participating site were to be sent to the Photobiology Unit in Dundee for calibration in the 3 month period prior to the start of subject recruitment.
- Centres could apply photopatches for either 24 or 48 hours prior to irradiation, according to local preference.
- Each centre could communicate with the coordinating centre in Dundee via one of two methods. Firstly, the results from all the centres in one country could be collated by a named PI who then communicated with Dundee (in the event, this did not happen from any centre). Secondly, individual PIs could communicate directly with Dundee. There was to be 3-monthly posting/faxing of completed subject proformas data to Dundee.
- The complete collated and analysed data was to be submitted for peer-reviewed publication as one document, but local data could be presented at local meetings.
- English was to be the language of data recording, communication and publication.

There was some productive debate about which topical NSAIDs should be included in the test series, and at which concentration they should be tested. This was decided within ten days of the initiation meeting via email communication between three European contact allergy clinicians (two of whom were at the meeting) who had the greatest experience of testing with these agents.

After the successful use of a paper proforma for recording subject data in the UK-wide study, it was agreed that this would most likely be the method employed in the EMCPPTS. Consensus was agreed that the following information would be present on the proforma: subject unique identification number; subject age; subject sex;

subject diagnosis; subject indication for testing; photopatches applied for 24 or 48 hours?; name and concentration of each organic UV absorber and topical NSAID; the ICDRG grading scale; the COADEX scale for assigning relevance.

7.3 Refining the protocol and proforma

Following the initiation meeting, the protocol was refined over the next five months. Subsequent drafts of the protocol were circulated to colleagues both in the Dundee department and the UK, seeking further expert opinion. It was felt that this process served as a "Quality Control" mechanism for detecting inaccuracies and generating constructive ideas. In these five months, news of the proposed EMCPPTS had been disseminated by attendees of the Amsterdam meeting to colleagues across Europe and greater than 40 interested PIs had signalled their potential interest in participating. In July 2007, the finalised protocol was sent via email to these individuals, who were named as PI's at their centre.

The protocol (Appendix 2) contained a copy of the initial proforma for recording subject data in an appendix. However, this required refining over a longer duration than the protocol itself, due to its pivotal role in the study and because of the subsequent advice taken from the data entry team in the University of Dundee HIC (see next section). Therefore, the finalised version of the proforma (Appendix 3) was not emailed to PIs until April 2008. To aid adherence to the same methodology, each PI was emailed a proforma on which their country and centre-specific numbers had been pre-entered. Although the majority of PIs followed this methodology, many needed intermittent email reminders of their country and centre numbers. A small number of PIs also continued to incorrectly use the initial, unrefined version of the proforma from the protocol throughout the duration of the study, despite intermittent email reminders attaching their centre-specific version of

the proforma. In retrospect, such confusion may possibly have been averted by only issuing the finalised protocol with a finalised proforma.

7.4 Data handling

When the UK PPT test study was conducted from the year 2000-2002, one area identified for improvement was that of data collection, entry and analysis. During that study the data obtained was entered into a non-secure and non-robust database by the clinician coordinating the study in Dundee, which was very time-consuming. Therefore, in July 2007, five months after the Amsterdam initiation meeting, it was decided to use the services of the University of Dundee HIC for the EMCPPTS. The main role of the HIC is to securely handle data from biomedical trials running in the University of Dundee and NHS Tayside.

Initially, the possibility of setting up an online data entry system, which could be accessed by all PIs in Europe via a secure password was discussed. Such an online proforma would have the great advantage of generating more standardised data for analysis by allowing only desired information to be entered onto a form in a specific manner. However, this idea was discounted as the HIC team advised that it would be relatively expensive to set up for a study recruiting 1,000 subjects. Additionally, all PIs (many of whom did not speak English as their first language) would have to be trained in using such a system, which would create delays and add to costs.

It was decided that a single sided A4 paper proforma would be used for data collection from participating centres. The main advantages of this system were that it was inexpensive and could be easily backed-up by photocopying. The main drawback was that PIs could fill it out incorrectly and/or omit data. This could lead to data loss and also generate additional work for the study coordinator vetting

proformas. The exact format of the proforma (Appendix 3) was shaped by discussions with the HIC team about the essential data to be captured and ease of data entry to the database. The database was set up by the HIC team in January 2009, six months after subject recruitment to the study had commenced. To aid the database set-up, a batch of "dummy" proformas were filled out and given to the HIC team to test the system. Refining the programme used to generate queries for data extraction from the database required liaison with the HIC team in April 2009. However, use of this initial programme had to be discontinued as it was not capable of running the required queries. Ultimately, to obtain meaningful results from the database required the combination of a different programme and transfer of selected data to spreadsheets for further, more time-consuming analysis.

7.5 Calibration of UVA meters

The PIs at all of the 44 participating centres who had signalled their intention to participate in the EMCPPTS were asked to send their UVA meters to the Photobiology Unit in Dundee for calibration at the start of December 2007. This was to ensure that all centres were irradiating the test sites with the same UVA dosages. The meters were then returned to the PIs by courier, with costs covered by the Dundee Photobiology Unit.

Within six months of requesting UVA meters for calibration, only 24 of 44 PIs had sent their meters to Dundee. It was decided not to pursue the remaining PIs who had not sent their meters, because of the possibility of irritating them with repeated email requests. Such irritation was adjudged to have carried the risk of causing them to withdraw from the study. This skill of sending tactful but focussed email requests a limited number of times became the standard method needed to try to keep the EMCPPTS project progressing over its four year duration.

7.6 Delivery of agents

As mentioned above, six months after the initiation meeting, 44 PIs had confirmed their intention to participate in the EMCPPTS. Therefore in August 2007, Chemotechnique Diagnostics Ltd were first contacted to discuss the preparation and delivery of the photopatch test agents to all centres. Unfortunately, the database containing the results of the study into the pilot irritancy study discussed in Chapter 4 (which was funded by L'Oreal Ltd) had been "locked" until study completion in October 2007. It was only after data analysis of these results in December 2007 that it became known that benzophenone-4 was the sole UV absorber that would need to be made up at a 2% concentration (as opposed to 10% for all other organic UV absorbers). However, when Chemotechnique Diagnostics Ltd were then given this information, they responded that it would take until April 2008 for the agents to be prepared and delivered i.e. another four months.

This additional delay of at least four months was not foreseen, but it was not appropriate to attempt to exert any pressure to expedite matters on Chemotechnique Diagnostics Ltd, given that they had agreed to fund 75% of the study. This delay necessitated intermittent email contact with all PIs, keeping them abreast of these unforeseen developments. In March 2008, Chemotechnique Diagnostics Ltd informed the Photobiology Unit in Dundee that it may be the end of April before the delivery of agents could take place. It was negotiated with them that half of the 25% of the agent costs not being funded by them would be transferred to them, in the hope that it would serve as an incentive to continue agent preparation.

After further delays, the PPT agents were eventually delivered to the PIs in the original 44 participating centres on 11th July 2008, almost one year after the centres had signalled a desire to participate. The initial batch of agents prepared by

Chemotechnique Diagnostics Ltd allowed a total of 56 sets to be delivered over the next 2½ years, as sets were used by PIs. In March 2010, with the study recruitment taking longer than anticipated, requests for replacement sets of agents continued to arrive via email from PIs. At this point, Chemotechnique Diagnostics Ltd informed the Photobiology Unit in Dundee that a new batch would need to be made up. Initially, they asked for a non-subsidised market price per set, which would have amounted to a prohibitively expensive £30,000 to re-supply all PIs. After negotiation, it was agreed that ten sets would be supplied for the usual market price of one to expedite completion of the study, an outcome in which both parties had a vested interest.

7.7 Application for ethical approval

In the UK PPT study in 2000, ethical approval was not sought or required because the investigation of PPT was judged to be "part of routine clinical care" for patients attending the participating centres. Therefore, to simplify and expedite proceedings, a similar approach was initially adopted when setting up the EMCPPTS in 2007. In the early versions of the draft protocol, the following statement was included: *"As the agents used in the sunscreen study are being used as part of the routine investigation of patients with an exposed site dermatitis, ethical approval will not be required. If you are in doubt about the situation within your own country, it is advised that you discuss it with the appropriate Ethics regulatory authority."* In retrospect, it should have been clear that pursuing such an approach would not be possible in the UK. This was because in the intervening years between the two studies (2000 and 2007), the regulation of clinical research within the UK had evolved rapidly, meaning more extensive authorisation from multiple bodies was required before any subject recruitment could proceed.

The submission for ethical approval for the EMCPPTS was made in September 2007 to the Fife and Forth Valley Research Ethics Committee (REC). This was a Type 3 REC, which could grant approval for the use of the same supporting documentation for the study in all UK centres. Three weeks after the submission, I attended the REC meeting at which the EMCPPTS was being reviewed and was questioned by committee members. By attending, any queries the REC raised regarding the study could be more rapidly answered and it allowed me an insight into the working of the REC procedures. The REC requested a few minor amendments to the Patient Information sheet (PIS) before ethical approval was granted for the Dundee site, six weeks after the initial submission.

In 2007, the process of submission to the REC required an electronic form to be completed and uploaded through the National Research Ethics Service (NRES) portal, which worked efficiently. In addition to the main submission, a shorter Site Specific Assessment (SSA) for each of the UK sites had to be part-completed online at the Dundee end. The NRES system required an email address for each PI in the UK, who was then automatically sent their part-completed SSA to complete and submit to their local REC. On the surface, this process appeared to be straightforward, but in actuality most UK PIs found the process rather time-consuming and confusing. To compound the problem, many PIs encountered difficulty when seeking help from their local ethics department on how to complete their SSA. Although the system was supposed to be a national one, each local ethics department decided on the appropriate action required for the SSA according to local guidelines. The overall result was long delays in obtaining ethical approval locally at several UK sites. Unfortunately, one UK-based PI withdrew from the study at this stage, citing the complexity of ethical approval as the main reason. The

time and work required to complete such a task highlighted that most full-time clinicians need to delegate such duties to others within their department. This can have direct financial implications for departments wishing to continue conducting research, e.g. by needing to employ a research nurse.

A notification of a "Substantial Amendment" was submitted to the REC in July 2008 when it was decided that the PIS would have to be sent via post to all clinic patients attending the Photobiology Unit in Dundee unit who *may* be eligible to participate in the study. This allowed potential participants to have at least 24 hours to read the PIS before making an informed decision as to whether to participate in the EMCPPTS at the time of their clinic attendance. In Dundee, this delayed the start of subject recruitment by a further two months, until September 2008.

It was not possible to determine if the rigorous ethical regulatory process adhered to in the UK was similarly enacted across all the other European countries involved. The legal framework relating to ethical approval in each country was different and for the coordinating centre in Dundee to ensure all centres had sought the ethical approval that was necessary in their respective country, would have been prohibitively expensive (e.g. by employing someone to travel to each of the 44 centres and facilitate the process in each centre). When it first became apparent that ethical approval would be required in the UK, the protocol wording was amended to the following phrase: *"An application for ethical approval to cover the multiple sites in the UK will be made. Similarly, approval from the Medicines and Healthcare Regulatory Authority (MHRA) will be sought. As regards other European centres, <u>if you are in doubt about the situation within your own country, it is advised that you discuss it with your Ethics regulatory authority.</u>"* It was felt

that this would be a reasonable way of communicating the need to consider the issue of ethical approval to all centres involved.

The precise number of European sites that sought or obtained ethical approval was not clear, but subsequent emails suggested that of the initial 44 centres, approval was sought in the following countries: Austria (2 of 2 sites); Belgium (1 of 2 sites); Denmark (1 of 1 site); Germany (3 of 4 sites); Hungary (1 of 1 site); Spain (2 of 6 sites). Email correspondence from Italy (2 of 2 sites) and Sweden (1 of 1 site) suggested ethical approval would not be required. No correspondence relating to ethical approval was received from the following countries: Greece, Holland, Republic of Ireland, Poland, Portugal and Switzerland.

The 11 centres in France which initially signalled an intention to participate were behind all other European centres in the processes of regulatory approval. The first email relating to a need to obtain ethical approval was in November 2008, four months after the agents had been delivered and subject recruitment had started elsewhere. The ethical submission throughout France was coordinated by a non-clinician attached to the Lille department, who began a submission in February 2009. It was only in May 2009, ten months after subject recruitment had started at other sites that email notification was received that a successful submission in France had been made. This significantly delayed the substantial recruitment of subjects by French centres. In the case of one French centre, email notification was received in May 2010 (22 months after subject recruitment had started elsewhere) to indicate that the first subject had been recruited at that centre.

7.8 Application for Research and Development approval

The organisation named as the study sponsor in the ethics submission was National Health Service (NHS) Tayside, the hospital trust in which the Dundee Photobiology

Unit operates. In 2007 in NHS Tayside, as well as ethics approval, approval to conduct a research study also needed to be sought and obtained from the Research and Development (R&D) department. The R&D department were responsible for ensuring that trial investigators conducted research according to the principles of the International Conference on Harmonisation (ICH) code of Good Clinical Practice (GCP). A second function of the R&D department was to evaluate the financial cost of using NHS Tayside staff members and property to conduct a research project, and if necessary seek a portion of the study funding to compensate for this.

The submission for R&D approval began in parallel with the ethics submission in September 2007. The first delay in obtaining R&D approval occurred in October 2007, when we were informed that the application would not be considered until there was notification from the UK Medicines and Healthcare Regulatory Agency (MHRA) that the EMCPPTS did not require a Clinical Trials Authorisation (CTA). The MHRA confirmed that no CTA was required because the 24 study agents prepared by Chemotechnique Diagnostics Ltd were not commercially available "finished products" and therefore the EMCPPTS was not classed as a Clinical Trial of an Investigational Medicinal Product (CTIMP). This notification from the MHRA was forthcoming within one month, so did not lead to a significant delay.

The next delay created by the R&D application process was the drafting by that department of a study agreement for all PIs in the UK and Europe to sign and return by post. The intended purpose of this contract was to ensure that all PIs acknowledged that they would conduct the study at their own centre according to the ICH GCP standards and that they would have indemnity in place locally. This contract was the R&D department's interpretation of what was necessary for the

EMCPPTS to comply with The Medicines for Human Use (Clinical Trials) Regulations 2004 Directive, which was the embodiment into UK law of the European Clinical Trials Directive (2001/20/EC).[3,4] The intention of the R&D department in this respect was laudable, however, in practice the process caused widespread confusion among most of the study PIs and resulted in a significant delay to subject recruitment.

The contract drafted by the R&D department was 11 sides of A4 paper in length, inclusive of two signature pages, and written in English. A list of the email and postal addresses of all PIs was supplied to R&D personnel, who initially emailed the contract to all UK PIs in November 2007. However, the lines of communication from the R&D department to the Photobiology Unit were not good and we were unaware that such emailing had taken place. It was only when a UK-based PI brought it to our attention in January 2008, because of the confusion it had caused between him and his local R&D department, that we were aware the process had started. All other UK PIs were then sent an explanatory email from the Photobiology Unit, asking them to sign and return the contract to the NHS Tayside R&D department. The R&D department then emailed the contract to all non-UK based European PIs in March 2008, after a preparatory email to the PIs from the Photobiology Unit. As many of these PIs did not speak English as their first language, this contract generated a chronic period of confusion among PI's that lasted until after subject recruitment began in July 2008.

In addition to the confusion caused by the contract, the R&D department initially informed the Photobiology Unit that subject recruitment would not be allowed to commence at any centre until they had received signed copies of the contract from all European centres. Had this been enforced rigidly, it would most likely have led

to the termination of the study, as it would have been extremely difficult to achieve this within a reasonable timescale. However, senior staff members within the R&D department were aware of the confusion that had been generated by the contract and subsequently conceded that this was not a practically workable proposition. The study was also allowed to commence recruitment prior to the return of all contracts because it was the core research project of this thesis and therefore had an educational and time-dependent component.

7.9 A major protocol violation

In June 2010, almost two years after subject recruitment had commenced, the Photobiology Unit were informed by a UK-based PI of a major protocol violation at their centre. The PI had delegated the running of the study to a colleague and had assumed that subject recruitment had been proceeding according to the protocol. However, it became apparent that although greater than 100 subjects had been recruited at that centre, none of them had signed the consent form for participation. In the Photobiology Unit, we immediately alerted the relevant personnel responsible for facilitating research in NHS Tayside, who offered guidance for this protocol violation.

Several actions were required, the first being the immediate suspension of further subject recruitment at the UK centre where the protocol violation occurred after liaison with their local R&D department. Secondly, the team performing the study at that centre were informed that they would have to undergo accredited ICH GCP training before the study could be allowed to re-start again at that centre (although ultimately it did not re-start). Finally, all the completed subject proformas from the centre that had been sent to Dundee were sent back, as the recruited subjects had not consented to the sharing of their personal study data. Likewise, the data from

these proformas which had been entered into the database by the HIC team in Dundee was permanently removed. At the outset of proceedings, the possibility of obtaining retrospective consent from these subjects was suggested by the research guidance personnel in Dundee. This would have entailed the PI at the centre writing to subjects to explain the situation and enclosing a consent form to be signed and returned. However, this approach was deemed non-viable, as the completed proformas had been anonymised and there was not a corresponding log from which subjects could be accurately identified.

The Fife and Forth valley REC was notified of this major protocol violation by letter, which also explained that subject recruitment period would need to be extended to compensate. The research facilitators in NHS Tayside also requested a "spot check" of consent practices across all UK sites, which entailed the PI at each centre sending in copies of the signed consent forms for 5% of the number of subjects they had recruited by that time. Fortunately, other PIs complied quickly with this request and no further anomalies relating to subject recruitment were discovered. Overall, the loss of over 100 subjects from the UK centre where the violation occurred led to extension of the recruitment period at all other centres by approximately three months.

7.10 Funding the EMCPPTS

The funding for the photopatch test agents used in the EMCPPTS were 75% contributed by Chemotechnique Diagnostics Ltd, with the remainder funded by a combination of L'Oreal Ltd and the Photobiology Unit in Dundee. Other costs (such as the courier costs for UVA meter calibration and the HIC team costs) were funded by the Photobiology Unit in Dundee. Neither of the two commercial companies had any influence on the outcome of the study, but both would have an

interest in the EMCPPTS being performed for different reasons. Firstly, L'Oreal Ltd developed and hold the patents on two of the "newer" organic UV absorbers (terephthalylidene dicamphor sulfonic acid and drometrizole trisiloxane) and would be interested in results which more clearly defined their allergenic and photoallergenic potential. Secondly, Chemotechnique Diagnostics Ltd would be interested in knowing which agents may be likely to form the basis of a future commercially available European Baseline photopatch test series.

It could be debated that incorporating the financial aid of such private companies into a research study conducted across independent higher education institutions creates a low level conflict of interest for the researchers. Indeed, it is true that some observers will always view the results of any such research with a degree of scepticism. However, the EMCPPTS demonstrates that it is possible, through patient and open dialogue with such companies, to complete projects of this scale which may otherwise not have been feasible. If, like the EMCPPTS, the outcome is truly unbiased, then collaboration with such sources of funding can be very fruitful. It is also clear that with the increasing regulation and paperwork needed to conduct such trials in the UK, that securing funding for additional research staff via flexible methods is likely to remain very relevant.

7.11 Other issues around conducting the EMCPPTS

The bulleted points below highlight various factors that arose during the four years that the EMCPPTS ran. Hopefully the identification of such issues may lead to a future multi-centre PPT study proceeding more smoothly.

- Emails containing updates of the total subject numbers recruited and reminders to send completed proformas to Dundee were sent out to all PIs at 3-6 monthly

intervals. This was necessary to ensure recruitment continued, but as mentioned above, had to be not so frequent as to irritate PIs.

- The information recorded on all proformas received in Dundee was vetted and if clarification over data was required, the PI concerned was emailed. Such clarification was a relatively common and time-consuming exercise and therefore, as a rule, only one enquiry email could be sent. Pursuing PIs with several emails at subsequent intervals was not possible due to the number of queries generated, and would also have risked irritating the PI involved. In most cases the PI would respond with the appropriate information, but there were some cases where no response was received, resulting in incomplete data capture.
- Despite the protocol and proforma specifying that a dose of 5 Jcm^{-2} UVA was to be used for irradiation of the PPT site, several German and Austrian centres used a dose of 10 Jcm^{-2} as standard. This was likely due to a long tradition of using this higher dose in these countries despite evidence that it could lead to false positive results.[5] Following email dialogue, these centres agreed to switch to using 5 Jcm^{-2} UVA. Similarly, in the process of vetting completed proformas, it was sometimes unclear as to the exact timing of photopatch application, removal, irradiation and reading. As an example, one centre was applying both sets of agents at the same time, removing and irradiating one set at 24 hours and then removing the covered set 24 hours later (i.e. 48 hours after application). As discussed in Chapter 1, this methodology introduced an unnecessary variable. Several centres had to be contacted by email to clarify such issues surrounding methodology.

- Several centres in Mediterranean countries, most notably Spain, suspend PPT in the summer months. This is necessary because the high ambient temperature causes the petrolatum vehicle to decrease in viscosity. As a result, it becomes difficult to ensure the vehicle and test agents remain within their originally applied position on the skin. Despite this suspension in testing, recruitment at such centres remained very good throughout the rest of the year.
- Of the original 44 PIs who agreed to recruit patients, two formally contacted the Photobiology Unit in Dundee to withdraw from the study after delivery of the test agents as they felt unable to fulfil the study requirements. However, another 12 received test agents, but did not recruit any patients and did not contact the Photobiology Unit in Dundee to express any difficulty in undertaking the study. The action of these PIs was disappointing, particularly as the test agents sent to their centres could have been used by other active centres, thereby reducing costs.
- After subject recruitment had commenced, two separate PIs independently raised the possibility of amending the protocol to include decyl glucoside, the surfactant used with methylene *bis*-benzotriazolyl tetramethylbutylphenol (Tinosorb M®) as a test agent in its own right. This followed the publication of reports of decyl glucoside being responsible for positive allergic responses in patients patch tested to Tinosorb M®.[6] Incorporating decyl glucoside as a test agent into the EMCPPTS, would indeed have been desirable, given the results obtained in the Chapter 4 pilot irritancy study. However, it was not feasible to alter the EMCPPTS protocol in such a major way after subject recruitment had commenced, as this would inevitably have delayed or caused suspension of the study.

Year	Month	Event	Significant delay / adversity
2007	February	Initiation meeting Amsterdam	
	March		
	April		
	May		
	June		
	July	Protocol finalised	
	August		
	September	Ethics submission	R&D submission
	October	Ethics approval	
	November		R&D contract sent to UK PIs
	December	UVA meters requested	Agents requested
2008	January	Proposed start of recruitment	R&D contract confusion arises in UK
	February		
	March		R&D contract sent to European PIs
	April	Proforma finalised	Proposed agent delivery
	May		
	June		
	July	Actual start of recruitment	Actual agent delivery
	August		
	September		
	October		
	November		
	December		
2009	January	HIC database set up	
	February	Proposed end of recruitment	Ethics submission starts in France
	March		
	April		
	May		Ethics approval in France
	June		
	July		
	August		
	September		
	October		
	November		
	December		
2010	January		
	February		
	March		
	April	New batch of agents prepared	
	May		
	June		Protocol violation at UK centre reported
	July		
	August		
	September		
	October		
	November		
	December		
2011	January		
	February	Actual end of recruitment	

Figure 7.1. The timeline of significant events and delays during the EMCPPTS.

The events described in this Chapter highlight that, although not easy, it was possible to conduct a large multi-centre study aimed at determining the relative frequency of PACD to several agents in common usage in Europe. Hopefully, by illustrating the difficulties that may be encountered for investigators, a future similar study may proceed more smoothly. The following Chapter outlines how the information obtained in the EMCPPTS, as well as information presented in other Chapters of this thesis, was of key importance in aiding the discussion about which agents should be present in a new European Baseline photopatch test series.

7.12 References

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