BACKGROUND

In early December of 2003 a meeting took place during the San Antonio Breast Cancer Symposium between a small number of European investigators and clinical research managers. The single agenda item was the impact of the European Union (EU) Clinical Trials Directive (CTD) 2001/20/EC on European clinical research.

The Irish contingent was particularly concerned because an early review of the first draft of the Irish government’s transposition of the CTD into Irish law identified a number of difficulties. One in particular would halt academic cancer clinical research in its tracks: the first draft stated that all medications in a clinical trial must be provided for free regardless of the origin of the study, be it academic or industry. The Belgian contingent was equally concerned for similar reasons. Subsequently, the “Save European Research Campaign” was born. One week later a Web site was launched, and to everyone’s surprise it took just 6 days for 1,000 clinical research professionals from across Europe to sign up in support.

*In the European Union, a “directive” is a type of legislation that binds Member States to specific objectives to be achieved within a certain time period, but lets the national government of each Member State decide the form and means of implementation.

CONTENTS

The EU Clinical Trials Directive More than One Year On: Where Are We Now? .......... 1
BIG Trials ............................................................ 12
New Trials........................................................... 17
TRANSBIG News ................................................ 18
Upcoming Events................................................ 18

This issue was made possible through the generous support in the form of an unrestricted educational grant from Schering-Plough.
It is well over a year now since the 1 May 2004 deadline for European Union (EU) Member States to transpose the EU Clinical Trials Directive (CTD) 2001/20/EC into national legislation. What has its impact been on clinical trials in Europe so far?

In answer to that question, this newsletter brings together several voices from within the BIG and TRANSBIG networks. The articles are arranged so as to begin with two pieces that provide both some overall context as well as quite clear opinions on the matter (B. Moulton, P. Therasse). These are followed by three reports on the practical experiences of groups from two regions in Europe, the Iberian Peninsula (E. Mahillo, J. Morales, J. Vazquez) and Germany (C. Hanne, G. von Minckwitz). Rounding out the theme is an article by the Federation of the European Cancer Societies (FECS) (K. Vandendael), with a report on its efforts to learn from the key constituencies and to bring them together to help resolve the problems that the legislation has created for academia in particular.

The articles speak for themselves. Has the objective of simplification and harmonization of clinical trials administration across EU member states been achieved? Has the EU become a more competitive environment for running clinical trials? Are patients better protected as result of the legislation? The answer is a resounding “No!” In fact, academic-led trials are considerably at risk through increased bureaucracy and financial burdens. While some collaborative groups may have the financial and personnel resources necessary to “tough it out,” others will likely not. The same holds for individual researchers, present and future. Some may have the wherewithal to continue despite the added challenges. But most academic researchers in Europe and their staff are already overworked (many conducting research in their “free” time), so the long-term prospect of managing heavy additional bureaucratic burdens that are of no apparent and justifiable benefit to either the quality of research conducted or to patients is likely to have a marked effect on the choices these professionals make. Moreover, new generations of potential researchers may find little incentive to embark on such a path, or will seek alternative environments (outside of Europe) to fulfil their ambitions. And where does this leave our patients?

We are, of course, finding ways to work within the new legislative environment, to which the reports from the groups and FECS testify. Ultimately, only time will tell whether we are able to put academic research in Europe back on track. But as pointed out by Brian Moulton, time is of the essence, and it is quickly running out.
Eventually this number would grow to over 3,000, and a press release on the subject was issued in mid-December 2003. A few days later, former Commissioner Philippe Busquin, at the time responsible for the Directorate General (DG) Research (the DGs are divisions within the central European Commission government structure), gave a speech to Institute National de la Santé et de la Recherche Medical (INSERM), the French medical and scientific community. He acknowledged two key facts central to this discussion. First, in the 10 years from 1990 to 2000, the investment in research in Europe by European headquartered pharmaceutical companies had dropped by 10% and, second, the upcoming CTD was going to be “problematic” for European investigators, placing further pressure on already limited resources.

While those in Ireland ultimately had some success in changing the final draft of the wording of its law so as to reverse the free drug stipulation for academic studies, and some other countries had similar victories in local battles, what is the overall state of play in this war?

THE CLINICAL TRIALS DIRECTIVE

The intention of the CTD to increase clinical trial patient protection was honourable, if misguided and unnecessary. Has the directive added anything to the protection of the European patient participating in a clinical trial? The answer is, quite simply, NO. Why? Because the vast majority of those presently engaged in conducting research have for many years already carefully protected their patients. Prior to the CTD, close to 100% of all patients participating in oncology clinical trials had first completed a fully informed consent process. This process always included patients being presented with a document averaging 10 pages that outlined their rights, insurance status, and alternative treatment pathways in plain language. The CTD has done nothing to change this process. In fact, it could be argued that from a patient rights perspective, the impact of the directive has been negative. The trend in the short to medium term has been a sharp reduction in clinical trial activity in Europe and, hence, a reduction in the opportunity for European patients to obtain access to research treatments after current best practice options have been exhausted. In cancer, the clinical trial option is particularly important.

HARMONISATION

Before the CTD, there was a broadly based Europe-wide acknowledgement of and adherence to the principles of good clinical practice (GCP) in clinical research. In concert with many similar organisations based in Europe, ICORG had ensured that all of its clinical trial work had met this standard for at least the previous 5 years. The situation today is considerably less harmonious, and to identify just a few examples is difficult. Despite the absolute deadline of 1 May 2004 for the implementation of the CTD, the Netherlands (as of August 2005) has yet to transpose the law. The requirement for academic research to provide medications for free varies from country to country. The process of ethical approval has become much more complex, with some countries moving to single national opinion, and others disbanding ethics committees with little or no warning and consequently leaving the status of prior approvals in limbo. The key element of drug safety reporting varies as well: in some countries, ethics committees are demanding very detailed reports within days of the event, while in other countries they are refusing to accept any safety reports in protest of being overwhelmed by reams of often duplicated safety information in the months since the CTD.

HOW HAVE ALL OF THESE CHANGES IMPACTED CLINICAL RESEARCH IN EUROPE?

To answer this question, let us look at the cornerstone of academic clinical research: the investigator-initiated study. This can have many formats, but the most common is where an investigator or group of investigators approach a drug manufacturer and seek modest support to examine the activity of their compound in a niche area, in a rare disease type, in patient subgroups, or in combination with other treatments or older agents for which there is no commercial imperative to develop the compound. The barriers to be overcome today in order to successfully launch and ultimately complete this type of study have multiplied exponentially.

The CTD sought to clearly identify, and some would say isolate, the “sponsor” of a study. The sponsor has been interpreted by those transposing the CTD into local member state law as the single individual (or entity) who must take the overall responsibility for the many aspects of the study. Elements of sponsorship include, to mention but a few from a long list, ensuring timely SUSAR (suspected unexpected severe adverse reaction) reporting, protocol compliance by all investigators, quality standards at all collaborating centres, and drug labelling and accountability. In academic, multi-centre and multinational trials, this was traditionally a collective responsibility. Only very few individual European investigators have the resources (financial and human) available to them to successfully manage all of these types of responsibilities in the context of a multi-site study.

Also, this role of sponsor now requires the investigator to have in place specific multi-centre sponsor insurance. In most member states in the past, the standard national hospital physicians’ insurance included clinical trial activities as long as the trial protocol was correctly followed, and malpractice insurance covered them when it was not. The new multi-centre responsibility demanded by the CTD is not covered in standard policies. This has resulted in an expensive process, whereby collaborative groups such as ICORG have had to negotiate and fund separate sponsor insurance policies to enable their members to safely take on the multi-site sponsor role. The most troublesome aspect of the
process of obtaining this insurance has been the demand by
the insurance companies to show a track record in clinical
trial management prior to receiving a quote. Many individ-
ual investigators and some collaborative groups will not
have formal records of clinical research management expe-
rience. This is a new insurance market and one hopes that
the conditions of entry will change. However, to comply
with the conditions of the insurance, the insured collabora-
tive group or investigator must have sufficient resources in
place to ensure that an adequate quality standard is main-
tained throughout all aspects of the study.
These are substantial barriers that many academic
groups and investigators have failed to negotiate. The result
has been a dramatic fall-off in investigator-initiated studies.
In summary, there are four main reasons why this type of
research is in such sharp decline:

- Investigators do not have the extra resources necessary
to manage multi-centre studies.
- Funding and/or resources are not available to complete
the process of obtaining adequate insurance or to com-
ply with the basic conditions of this insurance.
- The many new obstacles have resulted in many physi-
cians and scientists who are less than 110% committed
to the clinical research process (because of other profes-
sional obligations, for example), putting their research
aspirations on hold.
- Finally, and most importantly, the traditional supporters
of clinical research, ie, the pharmaceutical industry,
have—because of the uncertainty of the situation in
Europe—moved to new world regions to complete
investigator-led and company-driven research studies in
a timely fashion.

THE FIGURES

New clinical trial initiation is an obvious and widely accept-
ed barometer of clinical trial activity. In Sweden the submis-
sions for new trials are down by 25% since the 1 May 2004
CTD transposition date. In Ireland the figure is 50%, with
the academic submission rate estimated to be down by more
then 70%.

In May of 2005, at a meeting of the European Forum for
Good Clinical Practice (EFGCP) in Brussels, the European
Organisation for the Research and Treatment of Cancer
(EORTC) confirmed that its new study start-up rate was sig-
ificantly down. At the same meeting, the single largest
organisation funding academic-based cancer clinical
research in Europe, Cancer Research UK, confirmed that
their new study start-up rate was down by approximately
50%. At the same time, pharmaceutical giant F. Hoffman-La
Roche indicated that it had accrued approximately 50% fewer patients into its studies in Europe in 2004 than in 2003.
While it was explained that this was due to factors other than
the CTD, such as the completion of some large European
studies in 2003, it does beg the question of how easy it will be
to correct this overall trend in the more complex post-CTD
environment. Both Roche at the Brussels meeting and
GlaxoSmithKline a few days later in the American newspaper
USA Today indicated the recent successful expansion or
movement of research programs into Asia.¹

The early figures show that Europe has suffered as a region
as a result of the implementation of CTD 2001/20/EC. The
downward trend is obvious. The lack of a clear response from
those who formulated this directive is troublesome. At the
EFGCP meeting in May, it was obvious that both the unit in
charge of the CTD’s implementation, DG Enterprise, and the
one most affected by changes in the European research envi-
ronment, DG Research, were neither mapping the changes in
activity, nor were they seeking to act quickly to bring together
stakeholders to agree on a corrective action plan.

CONCLUSION

Europe has always been at a disadvantage in the medical
research arena, protected time for European investigators is
not commonplace, and clinical research infrastructure is
well down the list of priorities for European hospital man-
agers. But, despite these challenges, European investigators
have contributed much to the development of medical sci-
ence, especially—in recent years. The CTD has undoubtedly reduced the enthusiasm and commitment
of the middle-ground investigators, who make up approxi-
mately 60% of the research community. Because they are
essential to the future of clinical investigation in Europe, the
difficulties of the CTD need to be addressed as a matter of
urgency before this disenchanted group walks away entirely.

The solutions may not be difficult to put in place. In brief,
I suggest that the EU Commission mandate that all Member
States take out national academic clinical research insurance
policies under which any recognised research body within
that Member State can work, providing they comply with
basic conditions. The obvious second part of this is that each
Member State put into place a competitive program of grant
funding for those involved in clinical research, specifically in
order to employ clinical research management personnel to
comply with the conditions of the CTD.

The problem is the old enemy—time. Traditionally the
time frame for the EU Commission to achieve such an ini-
tiative has been measured in years rather than months; every
new research program opened in Asia is a missed opportu-
nity for Europe, and such a trend is not easy to reverse.

I hope that those responsible for monitoring the impact
of the CTD at the European Commission and Member State
levels acknowledge the problem and immediately act to ini-
tiate the process of repair.

REFERENCE

1. Schmit J. Costs, regulations move more drug tests outside USA.
USA Today. 18 May 2005.
Efficiency, Quality, and Bureaucracy: Not Always in the Same Bag!*

Dr. Patrick Therasse, MD, Director, EORTC Data Centre, Brussels

The unique role of academic research—and the potential damage inflicted by recent legislation—was amply demonstrated by a recent study using the oral alkylating agent temozolomide. The study has been credited with creating a new beginning for chemotherapy in brain tumours.

However, without the involvement of academics, it would never have happened. Arguably—despite this study showing that good academic trials produce data robust enough for the purposes of drug registration—it may not have happened today in the legislation-heavy world in which academics have to operate.

To go back to the past, temozolomide was initially developed by Cancer Research Campaign (now Cancer Research UK) and sold at an early stage to the pharmaceutical company Schering-Plough. The company tested the drug for the treatment of melanoma, and of brain tumours, but results were unexceptional and interest waned.

A joint European Organisation for the Research and Treatment of Cancer (EORTC)-National Cancer Institute of Canada (NCIC) group, led by Dr Roger Stupp (Universitaire Vaudois, Lausanne, Switzerland), refused to let the matter drop, however. Many drugs had been tried in the treatment of glioblastoma, but none had improved survival significantly. Dr Stupp's group wanted to look at the effect of combining temozolomide with radiotherapy.

No pharmaceutical company would be keen to invest the money necessary to test a disappointing drug on a rare tumour. But the EORTC-NCIC group—with no financial money necessary to test a disappointing drug on a rare tumour. But the EORTC-NCIC group—with no financial support—was amply demonstrated that basic GCP principles protect patients' safety and their interests. Further bureaucracy will serve no useful purpose and may mean that potential improvements and new treatments for many conditions go undiscovered or untested.

On-site monitoring would have added around Euro 2.5 million to the costs of the trial—quite beyond the means of academic groups. Yet this study suggests that it may not be necessary and should not be mandatory in all situations. Well-established academic networks can conduct important studies, produce good quality data, and attend to patient safety. Basic good clinical practice (GCP) principles are sufficient for this.

The tragedy is that many important studies—like this one—are unlikely to take place in today's climate. It is not impossible, but the barriers are higher than ever. The European Clinical Trials Directive would have increased the time and costs 3 to 4 times compared to 1999, when this study was initiated. It would take at least 2 years longer to complete—recruitment alone could take 2 years longer because activation of trials is now so difficult. Any changes that have to be made during a trial could easily add an additional 2 years because researchers have to renegotiate them with each regulatory authority.

Future patients are the losers in this situation. We have demonstrated that basic GCP principles protect patients' safety and their interests. Further bureaucracy will serve no useful purpose and may mean that potential improvements and new treatments for many conditions go undiscovered or untested.

REFERENCES


*This article appeared in issue 14 of the European Journal of Cancer.
Implementation of the EU Directive
2001/20/EC in Spain

Esther Mahillo, PhD, Manager-Coordinator, Spanish Breast Cancer Research Group (GEICAM)

Since 1 May 2004, the Royal Decree 223/2004 has been the governing law for conduct of clinical trials in Spain. There were a number of outstanding issues related to the genesis of this Royal Decree. For instance, oncology cooperative groups had the chance to submit suggestions to the Spanish Agency of Medicine regarding specific problems such as SUSAR (suspected unexpected serious adverse reaction) notifications by investigators, study drug provisions for academic-sponsored trials, or expected additional administrative burden. However, most efforts to reach an acceptable new scenario for academic research in Spain have failed.

In the last year, as a consequence of the implementation of Royal Decree 223/2004, the following has happened:

- The cost of a clinical trial insurance policy, compulsory in Spain, has increased by 48%.
- Institutional Review Board (IRB) fees have increased by 20%.
- The average number of hours needed in-house for IRB submissions have increased from 8 to 35 hours per site. The immediate budget impact is a 77% increase.
- The average number of hours needed in-house to prepare a clinical trial application for the Spanish Agency of Medicine has increased from 4 to 16 hours. The immediate impact on the budget is an increase of 75%.
- The average time to obtain the regulatory green light for a trial (IRB + Spanish Agency of Medicine) has increased from 62 to 123 days.

Now let us look at the impact of these figures on the activities of The Spanish Breast Cancer Research Group (GEICAM):

- In 2004, GEICAM investigators recruited 1,079 patients in clinical trials.
- During 2004, 16 breast cancer clinical trials, all sponsored by GEICAM, were active and enrolling patients.
- 9 clinical research associates (CRAs) were responsible for conducting 245 visits to 57 investigator sites, and were able to review 5,317 case report form (CRF) segments.

To absorb the costs associated with the legislative changes, GEICAM had a few different options:

- Increase GEICAM’s professional staff by 75% (while reducing salaries in the same proportion, as study budgets remain the same).
- Increase the salaries of present staff members by 75%, but require them, in exchange, to work 120 hours per week.
- Decrease research activities by 75%.

Obviously, only the last option is a realistic one. So, the immediate future for academic research in Spain is not clear. In our country, between 500 and 600 new clinical trials are launched every year. Only 20% are sponsored by investigators, and it must be pointed out that cooperative groups in Spain do not receive any financial support from the government.

Nevertheless, things are slowly changing. It seems our Health Authorities are now concerned about, and even empathetic to, the future of academia-sponsored research in Spain. Indeed, they are involved in the preparation of a “Guidance on Specific Modalities for Non-commercial Trials Referred to in the Commission Directive 2005/28/EC Laying Down the Principles and Detailed Guidelines for Good Clinical Practice.” We expect the final text to address most of our concerns and, so far, we believe we have succeeded in transmitting them to our Health Authorities.
SOLTI and the Clinical Trials Application under the New EU Regulations Regarding Clinical Research: The Iberian Experience in Practise, Step-by-Step

Dr. Josefa Morales and Dr. Josep Vazquez, on behalf of SOLTI (Grupo Español de Estudio, Tratamiento y otras Estrategias Experimetales en Tumores Sólidos)

INTRODUCTION TO SOLTI

SOLTI is a cooperative group dealing with clinical research in breast cancer in Spain and Portugal. SOLTI was established in 1995 and currently includes 24 centres across Spain and 1 centre in Lisbon. We are involved in 8 active trials, most of them multi-centre and multinational. The sponsors of these trials are other international cooperative groups, university departments, the pharmaceutical industry, and SOLTI. The group has an operations office to initiate and conduct clinical trials according to Good Clinical Practice and other regulations.

SOLTI has had experience in preparing and submitting Clinical Trial Applications (CTA) under the former regulations on clinical trials, and recently we had the opportunity to make a submission for a clinical trial according to the 2001/20/EC Directive as transposed into Spanish and Portuguese laws. The following discussion will share with you the processes we followed as well as the timelines and the workload required to initiate this trial.

INTRODUCTION TO THE NEW REGULATION

The aims of the 2001/20/EC Directive are to facilitate and harmonise the processes to establish and conduct clinical trials across the Member States and to make Europe more competitive vis-à-vis the other major world regions, for instance, the United States and Japan, as well as emergent countries, such as those in Eastern Europe and Asia.

So far, the perception of people involved in clinical research in Europe is that the aims of the Directive are not being met. Here we report the real world experience in two European Union (EU) Member States—Spain and Portugal—with respect to a CTA submission under the current legislation.

THE AZURE EXPERIENCE

The AZURE trial, “A randomised study to determine whether zoledronic acid adds to the benefits of chemotherapy and/or hormone therapy in the treatment of women with breast cancer,” is a multi-centre, multinational clinical trial sponsored by the University of Sheffield, led by Prof. R.E. Coleman, and included under the BIG umbrella (BIG 1-04). SOLTI is contributing to this trial with 9 centres in Spain (Clinica Universitaria de Navarra, Hospital Universitario Vall d'Hebron, Hospital Clinico Universitario de Valencia, Hospital Son Llatzer, Hospital Universitario 12 de Octubre, ICO del Hospital Doctor Josep Trueta, ICO Duran I Reynals, Hospital Clinico Universitario Lozano Blesa, Instituto de Oncologia Teknon), and one in Lisbon (Instituto Portugues de Oncologia).

The first step in the process of requesting authorisation from the Spanish competent authority, Agencia Española del Medicamento y Productos Sanitarios (AEMPS), and for the opinion of the Reference Ethics Committee, for the AZURE clinical trial was to sign an agreement between the University of Sheffield (sponsor) and SOLTI. With this agreement the sponsor transferred to SOLTI some trial-related duties including the management of the study in SOLTI centres. It also allowed SOLTI to act as representative of the sponsor in Spain and Portugal. Therefore, SOLTI would be able to submit the CTA to the competent authorities and Ethics Committees (ECs), hold the clinical trial insurance policy for these centres, and sign financial contracts with the corresponding management boards of those institutions.

The next step was to prepare all the required documents for the submission of the protocol to the AEMPS and to the ECs of the participating centres for their evaluation and approval. This was not an easy job because there were several tasks that had to be done in parallel and that had to be very well coordinated by SOLTI in order to save time during the authorisation process. Several parties were involved in the process of obtaining these documents:

- **The Investigators**, who had to sign and provide us with several documents, eg, protocol agreement, curriculum vitae, availability of adequate resources, personnel, and quality of the facilities to carry out the study in their respective centres, investigator’s commitment form, site management board authorisation, plus other centre specific requests.
- **The Ethics Committees**, which all have different document requirements. For example, ECs may ask for different
numbers of copies of documents like the protocol, the patient information sheet and informed consent form, the Case Report Forms (CRFs), the investigator’s brochure or Summary of Product Characteristics (SPC), etc. Other documents are required by all ECs; these include the declaration by the sponsor (or its representative) to provide all the study drugs—which is already mandatory as per our Royal Decree 223/2004 that regulates clinical trials—and the declaration of acceptance of the institution’s model of clinical agreement, among others. One EC from among the participating centres has to be chosen by the applicant to be the Reference EC, which will be the one to give a unique opinion about the trial. There are two types of local ECs in Spain: the ones that regulate one centre only and those that regulate several sites within the same autonomous community. The latter type normally simplifies things slightly because the applicant sends all the documents to one EC, regardless the number of sites, and this regional EC then gives the authorisation for all of them at the same time.

- The Regulatory Authority (AEMPS) always requires the same document package for the protocol authorisation. Fortunately, this package of documents is quite reasonable and not as large as the one required by some of the ECs.

There are also other issues that make the preparation of a CTA even harder today than under the previous legislation, including the translation of some documents into to the national and regional languages. Although our AEMPS allows the submission of the protocol in English, most of the Spanish ECs request the protocol in Spanish. On the other hand, our AEMPS and ECs require the submission of the European Medicines Evaluation Agency (EMEA) CTA form in Spanish (Word format) plus the CTA form in English (completed on the EMEA Web site and submitted in XML format).

Apart from that, in Spain there is a National Calendar for the submission of these documents to the ECs of all the participating centres in order to obtain the clinical trial authorisation. ECs meet just once a month, and submissions have to be done in parallel to all the ECs within the first 5 days of the month. If these timelines are not respected, the protocol evaluation will have to wait until the following month. The Reference EC should give a favourable/objection/ unfavourable opinion within 30 calendar days. If there are objections (just once), an additional 30 calendar days are needed because the ECs have to meet again before they are able to give the final opinion. To make things more complicated, it might happen that despite the favourable opinion of the Reference EC, some of the local ECs reject the authorisation of the protocol in their centres. In this case, the applicant would have to negotiate with these ECs to resolve the problems and obtain their approval.

Finally, we can submit the authorisation request to the ECs and to the AEMPS in parallel or send to the AEMPS later on. However, notification of the Reference EC’s favourable opinion and the agreement of the management board of the centre are necessary before the authorisation by the AEMPS can take place. The AEMPS gives authorisation within 10 days from the receipt of these documents.

For the Spanish sites, the SOLTI experience with the AZURE included submitting the AZURE authorisation request to the ECs and AEMPS on 1 September 2004. Because there were some objections that had to be solved, the final favourable opinion of the Reference EC was not received until 10 November 2004. The AEMPS then gave us the approval for the AZURE on 19 November 2004.

For the Portuguese site things were different because, at that time, the European Directive was not completely implemented in Portugal, despite the fact that it was mandatory to have done so in all EU Member States as of 1 May 2004. Therefore, the previous regulations had to be followed. We submitted the application to the ECs of the Instituto Portugues de Oncologia, in Lisbon on 3 August 2004, and we received the approval from the ECs and Administration Board of this centre on 24 October 2004. On 26 October, we sent these approvals to INFARMED (the Portuguese Regulatory Authority) to get the approval for the use of drugs in clinical trials. Unfortunately, some objections were raised on 23 November 2004, though we did manage to resolve them. Finally, SOLTI received the authorisation from INFARMED on 20 January 2005.

It took us several days to complete the CTA form for the Spanish EC and AEMPS because a large amount of the information regarding the investigational medicinal product had to be provided by the sponsor (University of Sheffield). It took us one additional day to complete the same information for the ECs and AEMPS in the Spanish format of the CTA form.

We did not have to complete the CTA for Portugal until later because it was not required. However, INFARMED requested the completion of the CTA form for the AZURE trial in the EMEA Web site on 21 February 2005. Because we already had all the information from the Spanish CTA form, we were able to do it within one day.

On 4 February 2005 the first patient from a SOLTI centre was enrolled in the AZURE trial. The first patient enrolled at an international level was included in England in September 2003. The recruitment rate at the international level has been 2,066 patients in 22 months, 68% of the total sample size required. For the SOLTI centres, 79 patients have been included within 6 months, which reflects 65% of the SOLTI commitment.

CONCLUSION

According to our experience, we can confirm as correct the perception that the EU Directive's aims have not been attained. The process to submit the CTA in the EU is now far more complex, bureaucratic, and time-consuming, and indeed timelines have not improved when compared to the old system, at least not in Spain. In addition, local regulations
are not fully harmonised across Member States, mainly due to the requests imposed by local authorities to carry out the CTA. From a positive standpoint, however, we believe that as time goes by we will adapt and be able to integrate the new requests, making the process easier. Harmonisation could also be achieved if every Member State improves its level of competitiveness with respect to its neighbours in order to attract international clinical trials, and if each Member State also makes an effort to make the process easier and faster. In the meantime, the burden of competitiveness in the new legislative environment depends on the strategies of the sponsors and potential for recruitment by the investigators, respectively.

Looking at the GCP 2001/20/EG EU Clinical Trials Directive for IITs in Germany

Cecilia Hanne, PhD and PD Dr. med. Gunter von Minckwitz, German Breast Group (GBG)

In Germany, the EU Clinical Trials Directive 2001/20/EC was introduced with the 12th amendment of the German drug law (12. AMG Novelle) and came into force in August 2004. Now, about 1 year since the implementation of the Directive, we summarize our experiences in the Federal Republic of Germany with respect to Investigator Initiated Trials (IITs), keeping in mind that the process of implementation is still ongoing.

Trials started before August 2004 can still be conducted according to previous legislation. Evaluating the new law, one has to consider that before the directive was implemented, many breast cancer trials were conducted according to ICH-GCP standards, including site initiation and independent source data verification (monitoring). So changes mainly refer to the clinical trial submission process and the observation of the trial conduct.

In Germany, multiple Institutional Review Boards (IRB) exist, one per each German state as well as almost one for every university hospital. Previously, a trial protocol had to be submitted to every IRB separately, and the outcome could be variable with respect to whether or not the protocol was accepted, suggested changes (leading to different versions of the protocol in the areas), and especially the point in time when approval was received. However, the positive vote of a local IRB allowed every investigator in the area to participate.

Today, the sponsor must submit the protocol to the primary IRB, which is the responsible IRB of the “coordinating investigator” (formerly “principal investigator”) of the study. In case of a multi-centre trial, the sponsor also has to submit a copy of the primary application to all other IRBs that are responsible for the participating investigators. In the evaluation process, these other IRBs can give advice to the primary IRB, mainly with regard to changes or fundamental ethical problems with the protocol. They also have to evaluate each co-investigator separately and to confirm that the site is suitable for participation.

However, this new process raises some difficulties with cooperative group trials, where investigators start participation throughout the whole accrual period of the trial. Therefore, the IRBs have agreed that an adequate number of other IRBs have to be included in the first submission (for example, 70% of potentially participating investigators). But even this appears not to be feasible in large-scale trials, and the late registration of investigators entails considerable paperwork. Moreover, at least 30 days are now needed before a new investigator can be approved, so that previous procedures (identifying a patient, becoming a participating site, entering the patient in the study within 1 week) are more feasible for conducting multi-centre trials. It should be noted that in practise, some IRBs still persist in requiring further documentation, as well as commenting on parts of the protocol before they start voting on sites. Today, once the paperwork for submission is complete and submitted to the primary IRB, there are 30 days for the review process to take place and the response to be issued. So the actual time for approval is neither shorter nor longer than it was before the directive. But this is because today much more time is spent on the paperwork before the actual submission is made. Prior to implementation of the directive, time was eaten up by the different meeting intervals of each IRB.

The German Ministry of Health (MOH—Bundesinstitut für Arzneimittel und Medizinprodukte—BfArM) formerly had to be notified about clinical trials being carried out and the participating sites. Submitting paperwork was necessary, but the MOH did not review clinical trials. Today, the MOH reviews the trials, the pharmaceutical compounds, etc. The changes requested by the MOH include mainly administrative aspects of the protocol to meet the requirements of the directive. However, this might change with the experience MOH personnel will gain over time.

At present, the time needed for MOH approval remains longer than before, and the administrative quality of trials might be improved by this review. Because the time frames for trial approval are established by the directive, these regulations introduce a certain stability to the process of planning and waiting for clinical trial approval. Nevertheless, the process has neither been simplified nor shortened. IITs car-
ried out by a single investigator without the operational help needed to complete the paperwork, in addition to the new legal responsibilities for a sponsor, are much more difficult to live up to than before the directive. So, in comparison with pharmaceutical company trials or trials that can be managed through a study group like the GBG, the number of trials submitted by single investigator sponsors has decreased since the implementation of the EU-Directive. Another important aspect is that the fees for submitting trial protocols have definitely increased under the new legislation. The GBG has, however, still managed to successfully submit 5 phase I-III IITs as a sponsor since August 2004.

To summarise our experience so far, we have come to the conclusion that today more time is necessary to obtain the regulatory approvals than before the directive, although the intervals for approval have at least become predictable. In addition, the cost of the process has become more expensive.

But our experience will continue to evolve: Recently, in July 2005, the 14th amendment passed the German parliament, thus especially touching issues like pharmacovigilance and compassionate use of drugs during in-patient treatment in clinical trials. These issues have not previously been regulated to a satisfactory degree by the legislative organs of the German government. Hospitalized patients will now be able to receive the conventional treatment within a trial and have it covered by the public health insurance system. However, it is still not clear if this will be also the case for outpatient care.

FECS Action on the Clinical Trials Directive (CTD)

Kathleen Vandendael, Executive Director, Federation of European Cancer Societies (FECS)

INTRODUCTION

The Clinical Trials Directive (CTD) has now been in place for well over a year and the concerns raised by the academic community in advance of its implementation are now being realized. FECS has continued to be involved (both with the EU institutions, the national competent authorities, and physicians and academics from its Member Societies) in collecting data about the problems caused by the introduction of the CTD and in trying to find solutions to ease its implementation and to guide its future progress once the Directive is reopened.

To recap, the CTD was conceived by the European Commission as a means of simplifying and harmonising the administration that governs clinical trials by establishing a transparent procedure and creating conditions to foster the effective coordination of clinical trials in the European Union (EU). In short, the CTD aims to provide an environment for conducting clinical research that protects participants without hampering the discovery of new essential medicines.

However, the CTD did not properly anticipate the very specific needs of noncommercial clinical trials, and the increased bureaucratic demands and increased financial burden brought about by the implementation of the CTD have caused considerable difficulties for academic trials in Europe.

MEETING AT THE EUROPEAN COMMISSION

In April 2005 FECS organised, jointly with the European Commission, a workshop with the 25 competent authorities and a panel of academicians to discuss the provisions of the CTD relevant to academic research. The meeting was chaired by Dr. Birka Lehmann of the Pharmaceutical Unit of DG Enterprise.

As a basis for the meeting, FECS had produced (in consultation with EORTC) a questionnaire designed to gain information on how national authorities may have developed specific provisions to take into consideration the specific issues relating to academic research since the CTD came into effect. The questionnaire was sent to academicians working in oncology in all 25 EU Member States as well as to the 25 competent authorities. Of the 25 competent authorities, 11 returned a completed questionnaire, as did investigators from 16 Member States.

FECS opened the meeting by giving an overview of the experiences acquired by different nations since the CTD implementation, underlining the main conclusions highlighted by the survey. Following this overview, short presentations giving country-specific and European perspectives on the implementation of the CTD were made by Dr. Richard Sullivan (Cancer Research UK), Dr. Denis Lacombe (European Organization for the Research and Treatment of Cancer, Belgium) and Dr. Miguel Martin (Hospital Universitario San Carlos, Madrid, Spain). All these contributors gave concrete examples of a reduction in the number of clinical trials being activated and an increase in the bureaucracy associated with running clinical trials since the CTD came into force last year. For example, the time for approval for clinical trials has doubled in Spain from 60 days to 120 days as a direct consequence of the CTD.

The four speakers agreed that academic clinical trials are essential for patients, the CTD has slowed down the clinical trial process to the detriment of patients, and academic clin-
ical trials in the EU are now jeopardized by a lack of competitiveness with non-EU countries.

The meeting then focused on three main discussion points: (1) the definition of a “sponsor” (2) the definition of an Investigational Medicinal Product (IMP) and (3) free access to marketed drugs.

**Definition of a “Sponsor”**

The CTD only foresees one sponsor for any clinical trial, and therefore does not reflect the reality of international academic research with its usual network of local sponsors/institutions. Because sponsors must bear a number of liabilities under the CTD, this part of the legislation raises many important practical and structural issues for multi-centre and multinational academic research, as well as for national trials in some cases. In the FECS survey only 2 countries of 19 had provided a national definition that differentiated commercial from academic trials for national studies. Some countries (8 of 19) made it compulsory to have one single sponsor across the EU for multinational trials. The remaining 11 countries interpreted the legislation as saying that one sponsor was not a requirement.

The European Commission’s legal representative at the meeting indicated that they had tried in the guidelines to clarify the single sponsor concept. For example, a number of parties may agree, in writing, to form an organisation, provided this is done in such a way that the collective agreement fulfils all the required roles and responsibilities of the sponsor. This “collective” sponsor is responsible for ensuring that the conduct of the trial and the final data comply with the CTD and the GCP (Good Clinical Practice) Directive.

**Definition of an “IMP”**

The CTD gives a very broad definition of an “IMP.” The way in which individual Member States interpret the wording of the CTD has two serious implications for academic research: (1) an increased financial burden because the IMP is supposed to be provided free of charge and (2) an increased bureaucratic burden because an IMPD (Investigational Medicinal Product Dossier) is supposed to be provided for each IMP. Academic research, by definition, has restricted financial resources and cannot face these new requirements. Of the 19 responding countries, 12 had not taken measures to clarify the definition of an IMP.

**Free Access to Marketed Drugs**

Sponsors are normally meant to provide the IMP free of charge, and the CTD does make allowance for specific national provision in this regard. However, due to the broad definition of an IMP, academic research comparing drug regimens with commercialized products could be under obligation to provide all these products free of charge, even when the products would have been standard therapy for the trial subjects. Of the countries surveyed, only 7 accepted to provide the already marketed drugs free of charge, that is, not to be paid for by the sponsor.

**MEETING OUTCOME**

From the results of the survey, and the personal experience of the academic representatives, it was clear that the interpretation and implementation of the CTD has been confused and inconsistent across the EU. This is primarily due to a lack of clear definitions in key areas of the CTD, but is also partly due to individual Member States not building on the inherent flexibility of the CTD to achieve a flexible and pragmatic approach.

The European Commission representatives stressed the fact that the legislation is now in force and therefore cannot be altered at the current time, but they did encourage Member States to look for ways in which they can make things easier for themselves within the framework of the Directive. They made a special point of explaining that the legislation can be interpreted and implemented in a very flexible manner and that individuals, institutions, and Member States should explore the boundaries of this flexibility. One example of this flexibility was in the definition of a sponsor, where some Member States have demonstrated considerable initiative in their interpretation of the Directive. Some Member States had also taken measures to ensure free access to marketed drugs, and in one Member State the government agreed to ensure that costs for marketed drugs were reimbursed by the State. This flexibility also extends to industrial support for noncommercial trials, where the provision of medicinal products free or at reduced costs by industry will not disqualify the trial from being regarded as a noncommercial clinical trial.

**GOING FORWARD**

The UK’s representative at the meeting, Brian Davis, (Medicine and Healthcare Products Regulatory Agency) praised FECS for its efforts and contribution to improving the implementation of the CTD and said that the results of the FECS survey would be used to inform the debate within the Clinical Trials Facilitation Group (CTFG). In the meantime the Chair of the CTFG, Martyn Ward, asked FECS to provide clear guidance with regard to which issues should be addressed as a matter of priority, something which FECS is now identifying. FECS is also in the process of seeking to obtain completed questionnaires from those competent authorities who have not responded so far. Since 25 April, three additional competent authorities have replied with details of the implementation of the CTD in their countries.

The European Commission has indicated that another meeting will be held in 2006 to assess the progress made in
the implementation of the CTD, with respect to noncommercial clinical trials, and to address those problems that are still outstanding. In the meantime, the European Commission will produce a draft with guidance on several important issues such as the manufacturing of drugs, the importation of drugs, and the requirements concerning documentation.

**BIG Trials**

**BIG 2-03/GBG 29: Prospective Register Study of the German Breast Group (GBG) for Diagnosis and Treatment of Breast Cancer in Pregnancy**

*Dr. med. Sibylle Loibl (Principal Investigator, GBG) and Susanne Wüsthoff (GBG)*

**PURPOSE**

Breast cancer complicating pregnancy is a rare situation. However, among malignancies during pregnancy, breast cancer is the most common for women over the age of 25. Little is known about the true incidence in Germany and other parts of Western Europe. We have therefore initiated a trial to collect data—prospectively as well as retrospectively—to help assess diagnostic, treatment, maternal, and foetal outcome during pregnancy. The primary endpoint is foetal outcome 4 weeks after delivery. Secondary endpoints include maternal outcome, pregnancy outcome, diagnostic procedures used, and the biology of the tumour. A flow sheet for the treatment is provided and the acceptance of these guidelines will be evaluated.

**ACCRUAL**

The trial has been initiated in the German Breast Group but extension throughout Europe (under the umbrella of the Breast International Group) is warranted.

Status (as of September 2005): Participating centres, 21; number of patients, 51.

**PRIMARY ENDPOINT**

Foetal outcome 4 weeks after delivery

**SECONDARY ENDPOINTS**

- Maternal outcome of pregnancy
- Stage of and biological characteristics of breast cancer
- Breast cancer therapy (treatment, response to chemotherapy, type of surgery)
- Sensitivity and specificity of diagnostic procedures (palpation, ultrasound, mammogram)
- Outcome of the newborn after 5 year of therapy
- Outcome of breast cancer 5 years after diagnosis

**INCLUSION CRITERIA**

- Patients with histologically confirmed breast cancer who are pregnant
- Informed consent for data collection
- Karnofsky Index > 70%
- Patient suitable for surgery and chemotherapy
- Pregnancy without complications

**STUDY PERFORMANCE**

Every pregnant patient with histologically confirmed breast cancer should be informed about the register study. After written informed consent for data gathering has been given, the registration form should be filled out completely and sent to GBG/ SKM. Anonymized data will be collected in a database. A retrospective collection of data on already treated patients can also be done.

**THERAPY**

A flow sheet of diagnosis and treatment, which is not compulsory, is provided to guide the investigator.
DURATION

5 years of follow-up per patient

DATA MANAGEMENT

The central data gathering and the analysis will be done by GBG and SKM, Wiesbaden.

STATISTICS

Data should be analysed in a descriptive way.

PARTICIPATING COUNTRIES

Germany, Belgium

FUNDING AND ORGANIZATION

Funding is guaranteed by the non-profit foundation BANSS-Biedenkopf.

Groups interested in participating in the trial should notify Dr. Sibylle Loibl, <loibl@em.uni-frankfurt.de or loibl@germanbreastgroup.de>, or Susanne Wüsthoff, <Wuesthoff@germanbreastgroup.de>, at the German Breast Group (phone: +49-6102-79874-19) or at the University Hospital Frankfurt (phone: +49-69-6301-7024). Please also inform Livia Meirsman at the BIG office <livia.meirsman@bordet.be>.

Additional information and necessary documents regarding BIG 2-03 (Protocol—including flow sheets for therapy, patient information, informed consent—and Case Report Forms) are available for download at <www.germanbreastgroup.de/pregnancy>.

PLEASE HELP US TO REFINE OUR MAILING PROCEDURE...

Fax this form to BIG at +32 2 541 3199. Please print clearly

I have received this by post, but would prefer to receive future newsletters via e-mail.

Name: _________________________________________________________________________________________

Affiliated BIG group (if any): _______________________________________________________________________

E-mail address: __________________________________________________________________________________

I have received this newsletter via e-mail, but would prefer to receive future newsletters as hard copy.

Please provide:

Name: __________________________________________________________________________________________

Institution: _____________________________________________________________________________________

Address: ________________________________________________________________________________________

If you know of colleagues that would also like to receive this newsletter, please provide:

Name __________________________________________________________________________________________

Institution ______________________________________________________________________________________

Mailing or email address ___________________________________________________________________________

If you wish to be removed from our distribution list, please provide:

Name __________________________________________________________________________________________

Institution ______________________________________________________________________________________

If there are any other problems (mistakes in your postal address, etc), please provide us with full details.

_______________________________________________________________________________________________

_______________________________________________________________________________________________

_______________________________________________________________________________________________
BIG 1-05/IBCSG 32-05: Chemotherapy Adjuvant Study for Women at Advanced Age (CASA)

Phase III Trial Evaluating the Role of Adjuvant Pegylated Liposomal Doxorubicin (PLD, Caelyx®, Doxil®) for Women (age 66 years or older) with Endocrine Nonresponsive Breast Cancer Who Are NOT Suitable for Being Offered a “Standard Chemotherapy Regimen”

Coordinating Group: International Breast Cancer Study Group (IBCSG)

The CASA trial was distributed to interested centres and groups for Ethical Committee review and approval in early August. Interested groups should contact the IBCSG Coordinating Center in Bern, Switzerland, to receive the protocol (contact trial coordinator Melanie Strausak by E-mail: ibcsg32-05_CASA@ibcsg.org; phone: +41 31 389 93 91; fax: +41 31 389 93 92). There will be a CASA Investigators meeting during ECCO 13 on November 1, 2005 at 7:30 pm. Interested investigators should contact the IBCSG Coordinating Center for details.

The CASA trial is for older women (66 years of age or older) with histologically proven, resected breast cancer. The disease must be classified as endocrine nonresponsive, and patients must not be candidates for endocrine therapy or for an adjuvant chemotherapy program that includes a “standard” anthracycline-containing chemotherapy regimen. The overall aim of the CASA study is to investigate the role of PLD as adjuvant chemotherapy for older postmenopausal women for whom chemotherapy is indicated, but standard regimens, derived from trials in younger women, are assumed to be too toxic or inconvenient.

The two randomisation options of the CASA trial (Figure 1) enable physicians and patients to choose which control group (nil or low dose cyclophosphamide and methotrexate [CM]) is appropriate for a given patient, while the experimental treatment, pegylated liposomal doxorubicin (PLD) is part of both options.

**Figure 1:** Timing of randomisation: Due to the hypothesized benefit of early initiation of chemotherapy for patients with endocrine nonresponsive breast cancer, randomisation and commencement of chemotherapy (if assigned) should begin as soon as possible following surgery, but no later than 16 weeks. Chemotherapy regimens are 16 weeks in duration. PLD is given as 20 mg/m² iv x 8 doses (delivered every 2 weeks). Low-dose, metronomic CM is given as cyclophosphamide 50 mg/day orally continuously for 16 weeks; methotrexate 2.5 mg/twice a day orally days 1 and 4 of every week for 16 weeks.

**CM** = cyclophosphamide plus methotrexate; **PLD** = pegylated liposomal doxorubicin.
## Ongoing BIG Trials

<table>
<thead>
<tr>
<th>BIG Trial</th>
<th>Coordinating Group</th>
<th>Participating Groups</th>
<th>Question Asked/Primary End Point</th>
<th>Target No. Pts</th>
<th>Accrual as of August 2005</th>
<th>Pharma Partners</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-98/Young patients/ EORTC 10002</td>
<td>EORTC</td>
<td>GBG, IBCSG</td>
<td>Attitude toward risk of loss of fertility related to adjuvant therapies in patients with early breast cancer aged &lt; 35?</td>
<td>385</td>
<td>159</td>
<td>NA</td>
</tr>
<tr>
<td>1-00/p53 EORTC 10994</td>
<td>EORTC</td>
<td>ACCOG, SAKK, SBCG</td>
<td>P53 status and response to anthracyclines or taxanes?</td>
<td>1,850</td>
<td>1,440</td>
<td>Grants from Sanofi-Aventis and Pfizer; EORTC is sponsor</td>
</tr>
<tr>
<td>1-01/ HERA/BO 16348</td>
<td>BrEAST</td>
<td>20 BIG groups, 10 Roche-affiliated groups, plus approx. 100 independent centres</td>
<td>Comparison of 1 year vs 2 years vs no Herceptin® in women with Her2 + primary breast cancer who have completed adjuvant chemotherapy?</td>
<td>4,482</td>
<td>5,102*</td>
<td>Roche</td>
</tr>
<tr>
<td>1-02/ IBSCG 27-02/ Locoregional relapse</td>
<td>IBSCG</td>
<td>ABCSG, ANZ BCTG, BOOG, GBG centres, GECIM, NSABP</td>
<td>Benefit of adjuvant chemotherapy for radically resected locoregional relapse of breast cancer?</td>
<td>977</td>
<td>29</td>
<td>NA</td>
</tr>
<tr>
<td>2-02/SOFT/ IBSCG 24-02</td>
<td>IBSCG</td>
<td>ANZ BCTG, BrEAST, CEROUG, DBGC, EORTC, GOCCCHI, ICR-CTSU, NCIC-CTG, NCI, BCSG, SAKK, SBCG, TBCT, WMBG, YBCRG</td>
<td>Benefit of ovarian suppression given in addition to tamoxifen or aromatase inhibitor in ER+ patients who receive CT and resume menses afterwards?</td>
<td>3,000</td>
<td>267</td>
<td>Pfizer</td>
</tr>
<tr>
<td>3-02/TEXT/ IBSCG 25-02</td>
<td>IBSCG</td>
<td>ANZ BCTG, BrEAST, ICR-CTSU, SAKK, TBCT</td>
<td>Benefit of tamoxifen vs aromatase inhibitor for ER+ patients receiving GnRH analogue?</td>
<td>1,845</td>
<td>470</td>
<td>Pfizer</td>
</tr>
<tr>
<td>4-02/ PERCHE/ IBSCG 26-02</td>
<td>IBSCG</td>
<td>ANZ BCTG, BrEAST, ICR-CTSU, SAKK, SBCG, TBCT</td>
<td>Is CT necessary for low-risk premenopausal endocrine-responsive patients?</td>
<td>1,750</td>
<td>12</td>
<td>Pfizer</td>
</tr>
<tr>
<td>5-02/IBIS II</td>
<td>IBIS</td>
<td>ANZ BCTG, BOOG, DBGC, GBG, NCRI BCSG, SAKK, SBCG</td>
<td>Effectiveness of anastrozole vs placebo in preventing breast cancer in healthy, high-risk postmenopausal women and comparison between tamoxifen and anastrozole in postmenopausal women with DCIS?</td>
<td>10,000</td>
<td>955</td>
<td>Astra Zeneca, partial support (unrestricted educational grant)</td>
</tr>
<tr>
<td>2-03/GBG 29</td>
<td>GBG</td>
<td>ABCSG, BOOG</td>
<td>What can we learn about the diagnosis, treatment, and maternal/foetal outcome of patients with breast cancer during pregnancy (prospective register study)?</td>
<td>1,500</td>
<td>51</td>
<td>NA</td>
</tr>
<tr>
<td>1-04/AZURE NCRI BCSG / U. Leeds Trials Unit</td>
<td>NCRI BCSG</td>
<td>ACCOG, GOFIRC, ICORIG, ICR-CTSU, VCOG, WMBG, YBCRG</td>
<td>Benefit of zoledronic acid in (neo)adjuvant setting for improving bone metastasis and overall DFS in stage II/III breast cancer patients?</td>
<td>3,500</td>
<td>2,273</td>
<td>Novartis</td>
</tr>
<tr>
<td>4-04/ICE</td>
<td>GBG</td>
<td>WSG</td>
<td>What is the role of adjuvant chemotherapy; ibandronate with or without capecitabine in elderly patients with early breast cancer?</td>
<td>1,394</td>
<td>317</td>
<td>Roche/Astra Zeneca</td>
</tr>
<tr>
<td>1-03/ REACT/ ICCG C/20001, GBG 27</td>
<td>ICCG/GBG</td>
<td>BOOG, CEEOG, DBGC, GEOCO PERU, GOCCCHI, ICORIG</td>
<td>Benefit of 2 years adjuvant chemotherapy with celecoxib compared with placebo in primary breast cancer patients?</td>
<td>2,590</td>
<td>1</td>
<td>Pfizer</td>
</tr>
<tr>
<td>3-05/ GBG 26 / TBP</td>
<td>GBG</td>
<td>BOOG</td>
<td>Benefit of capecitabine with Herceptin® (H) in patients with HER2+ metastatic breast cancer and progression after previous (H) treatment?</td>
<td>482</td>
<td>88</td>
<td>Roche</td>
</tr>
<tr>
<td>2-04/ SUPREMO ACCOG / CCTT</td>
<td>ACCOG / CCTT</td>
<td>ANZ BCTG, CEEOG, EORTC, GEOCO PERU, HISS, ICORIG, JBCRG, NCIC CTG</td>
<td>What is the role of adjuvant chest wall irradiation in “intermediate-risk” operable breast cancer following mastectomy and axillary clearance?</td>
<td>3,500</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td>37,055</td>
<td>11,124</td>
<td></td>
</tr>
</tbody>
</table>
## Soon-to-Start/Planned BIG Trials

<table>
<thead>
<tr>
<th>BIG Trial</th>
<th>Coordinating Group</th>
<th>Participating Group</th>
<th>Question Asked</th>
<th>Target No. of Patients</th>
<th>Pharma Partners</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-04/ MINDACT/ EORTC 10041</td>
<td>EORTC</td>
<td>ABCSG, ABS at BASO, ACCOG, BOOG, DBCG, GBG, GEOC PERU, GOCCHI GOIRC, HBSS, IBCSG, ICOIRG, ICR-CTSUS, NCI RC BCSCG, SAKK, SBCG, SOITI, WSG, YBCRG</td>
<td>Will gene profile signature be a better prognostic tool to help in adjuvant decision-making than traditional clinical/pathological factors in node-negative breast cancer patients?</td>
<td>6,000</td>
<td></td>
</tr>
<tr>
<td>1-05 CASA / IBCSG 32-05</td>
<td>IBCSG</td>
<td>ANZ BCTG, EORTC, GBGOG, GEOC PERU, GOCCHI, ITMO, MOSG, SAKK, SBCG</td>
<td>Role of adjuvant Pegylated Liposomal Doxorubicin (PLD, Caelyx®) for women (age 66 years or older) with endocrine nonresponsive bc NOT suitable for “standard” CT?</td>
<td>1,296</td>
<td>Schering-Plough</td>
</tr>
<tr>
<td>2-05 ACTION</td>
<td>ICR-CTSUS</td>
<td>ACCOG, BOOG, NCI RC BCTG, YBCRG</td>
<td>CT versus non CT for older ER negative / poor patients (aged ≥ 70)?</td>
<td>1,000</td>
<td>Under negotiation</td>
</tr>
</tbody>
</table>

**Total 8,296**

---

## Closed BIG Trials

<table>
<thead>
<tr>
<th>BIG Trial</th>
<th>Coordinating Group</th>
<th>Participating Groups</th>
<th>Question Asked</th>
<th>No. of Patients</th>
<th>Reason for Closure</th>
<th>Pharma Partners</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-97/ MA.17</td>
<td>NCIC CTG</td>
<td>EORTC, IBCSG, TBCI</td>
<td>Benefit from letrozole (5 yr) after 5 yr of tamoxifen?</td>
<td>5,187</td>
<td>Reached target accrual; study outcome positive</td>
<td>Novartis</td>
</tr>
<tr>
<td>2-97/ ICCG 13/96</td>
<td>ICCG</td>
<td>ABCG, ANZ BCTG, CEEOG, DBCG, EORTC, FBSS, GEAG, GEICAM, GOIRC, GONO, IBCSG, ICOIRG, ITMO, NBCCG, NWEG, SBCG, US Oncology, WCTN, YBCRG</td>
<td>Tamoxifen → exemestane: superior to tamoxifen alone?</td>
<td>4,743</td>
<td>Reached target accrual; study outcome positive</td>
<td>Pharmacia</td>
</tr>
<tr>
<td>3-97/ HABITS</td>
<td>SBCG</td>
<td>EORTC (individual centres), GOCCHI, IBCSG</td>
<td>Hormone replacement therapy: safe after radically treated in situ, stage I or II breast cancer (&lt; 4 positive nodes)?</td>
<td>447</td>
<td>Following IDMC recommendations</td>
<td>NA</td>
</tr>
<tr>
<td>1-98/ IBCSG 18-98</td>
<td>IBCSG</td>
<td>DBCG, FBSS, Novartis</td>
<td>Sequencing of tamoxifen/letrozole or letrozole/tamoxifen superior to either agent alone?</td>
<td>8,028</td>
<td>Reached target accrual; first analysis positive</td>
<td>Novartis</td>
</tr>
<tr>
<td>2-98/ BrEAST 315</td>
<td>BrEAST</td>
<td>ABCSG, DBCG, GEICAM GOCCHI, IBCSG, ICOIRG, SBCG</td>
<td>Incorporation of Taxotere® in sequence or combination with Adriamycin: benefit to patients?</td>
<td>2,887</td>
<td>Reached target accrual</td>
<td>Aventis</td>
</tr>
<tr>
<td>4-98/ EORTC 10963/ PEAT</td>
<td>EORTC</td>
<td>DCRC, ICGG, YBCRG</td>
<td>Inhibitory effect of perioperative Faslodex® on development of metastasis, measured by DFS and OS?</td>
<td>20</td>
<td>Low accrual</td>
<td>Astra Zeneca</td>
</tr>
<tr>
<td>2-00/ EORTC 10974/ Lamanoma</td>
<td>EORTC</td>
<td>CEEOG, GOCCHI, ICGG</td>
<td>Benefit of conservative local therapy (vs mastectomy) in locally advanced breast cancer?</td>
<td>23</td>
<td>Low accrual</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Total 21,335**

*Accrual closed, but trial ongoing for 12-month versus 24-month comparison.

ABCG = Argentine Breast Cancer Group; ABCSG = Austrian Breast Cancer Study Group; ABS at BASO = Association Breast Surgeons at British Association of Surgical Oncology; ACCOG = Anglo-Gallic Cooperative Oncology Group; ANZ BCTG = Australian New Zealand Breast Cancer Trials Group; BIG = Breast International Group; BOOG = Dutch Breast Cancer Trialists’ Cooperative Group; BrEAST = Breast European Adjuvant Studies Team; CEEOG = Central and East European Oncology Group; CCTT = Cancer Clinical Trials Team (formerly Scottish Cancer Therapy Network); CT = chemotherapy; DBBCG = Danish Breast Cancer Cooperative Group; DCIS = ductal carcinoma in situ; DFS = disease-free survival; EORTC = European Organization for the Research and Treatment of Cancer; ER+ = estrogen receptor positive; FBSS = French Breast Study Group; GBG = German Breast Group; GBGOG = German Breast Cancer Study Group; GEAG = German Exemestane Adjuvant Group; GEOC PERU = Grupo de Estudios Clinicos Oncologicos Peruanos (formerly SPOM, Sociedad Peruana de Oncologia Médica); GEICAM = Grupo Español de Investigacion en Cancer de Mama; GtRH = gonadotropin-releasing hormone; GOCCHI = Grupo Oncologico Cooperativo Chileno de Investigacion; GOIRC = Italian Oncology Group for Clinical Research; GONO = Gruppo Oncologico Nord-Ovest; HBSS = Hellenic Breast Surgical Society; IBCSG = International Breast Cancer Study Group; IBS = International Breast Cancer Intervention Study Group; ICGG = International Collaborative Breast Group; ICGO = Israeli Clinical Oncology Group; ICORG = Irish Clinical Oncology Research Group; ICR-CTSUS = Institute of Cancer Research, Clinical Trials and Statistics Unit; IDMC = Independent Data Monitoring Committee; ITMO = Italian Trials in Medical Oncology; NA = not applicable; NBCCG = Norwegian Breast Cancer Group; NCI RC BCSCG = National Cancer Institute of Canada, Clinical Trials Group; NCI RC BCTG = National Cancer Research Institute Breast Clinical Studies Group; NSABP = National Surgical Adjuvant Breast and Bowel Project; NWEG = North West England Cancer Group; OS = overall survival; SAKK = Swiss Group for Clinical Cancer Research; SBCG = Swedish Breast Cancer Group; SOITI = Grupo Español de Estudio, Tratamiento y otras Estrategias Experimentales en Tumores Solidos; TBCI = The Breast Cancer Intergroup of North America; VCOG = Victorian Cooperative Oncology Group; WCTN = Wales Cancer Trials Network; WMBG = West Midlands Breast Group; WSG = Westdeutsche Studien Gruppe; YBCRG = Yorkshire Breast Cancer Research Group
There are substantial preclinical and numerous circumstantial data indicating that HER2+ ER+ breast cancer is less responsive to tamoxifen than HER2–ER+ disease. The preclinical data also indicate that this resistance is not replicated with oestrogen deprivation and limited results from some neoadjuvant studies with aromatase inhibitors support this. It is therefore not clear whether Herceptin will be of added benefit in HER2+ ER+ patients treated with aromatase inhibitors. The HELTH study aims to address this question. The trial protocol is still under final discussion, but draft details are as follows.

The study will randomize 180 postmenopausal patients with HER2+ ER+ primary breast cancer that are considered suitable for endocrine neoadjuvant therapy to receive either letrozole alone or letrozole + Herceptin for 4 months prior to surgery and 8 months after surgery. Patients on the letrozole alone arm will be offered 12 months postoperative Herceptin. Core-cut biopsies will be taken before treatment, after 2 weeks of treatment and at surgery. The primary clinical endpoint will be clinical response and the primary biomarker endpoint will be Ki67. A spectrum of other markers will be analyzed to determine the phenotype of disease that is responsive/resistant to these therapies.

There will be an interim analysis after about 30% of the patients have been entered; at this point, the feasibility of the trial will be considered and the Data Monitoring Committee will review the clinical response and Ki67 data according to prespecified guidelines.

It is clear that this will be a difficult study to recruit to since ER+HER2+ patients are uncommon. The large BIG network is therefore ideal and very important to utilize for this targeted therapy trial. A questionnaire will be circulated to BIG groups to allow the identification of interested centres with sufficient eligible patients.

The trial will be sponsored by Novartis and the data and trial coordination will be performed at the Institute of Cancer Research, London, by Dr. Judith Bliss and Dr. Lindsay Johnson. The Clinical Principal Investigator is Professor Ian Smith and Biological Principal Investigator is Professor Mitch Dowsett.

Certainty in ER and HER2 diagnostics is essential for the validity of this study. Centralized testing would be preferable but is considered impractical for this international trial in which rapid return of results is required. A quality assurance tissue array will therefore be constructed and sections will be circulated to prospective centres prior to initiation. Retrospective central testing will also be performed on the pretreatment core-cut and reviewed alongside the local result after 15% trial entry to ensure the appropriateness of this approach.

Finally, discussions are now underway for a similar adjuvant trial for older women with ER+ HER2+ disease who would not be considered for chemotherapy, to determine if there is benefit in adding Herceptin to an aromatase inhibitor, based on the dramatic results of the HERA trial.
TRANSBIG News

TRANSBIG\(^1\) and MINDACT preparation activities are ongoing and will be reported on in future issues. In the meantime, please consult our website <www.breastinternationalgroup.org> for further information, or direct inquiries to <transbig@bordet.be>

\(^1\)TRANSBIG is a translational research network founded by BIG in 2004. It is partially funded by the European Commission, the Breast Cancer Research Foundation, the Prix Mois du Cancer du Sein, and the Jacqueline Seroussi Memorial Foundation for Cancer Research. The funding organizations are not to be held responsible for any of the views expressed by TRANSBIG consortium partners or BIG/TRANSBIG staff.

Upcoming Events

Conference Calendar

2005

Lynn Sage Breast Cancer Conference
October 6–9, 2005
Chicago, Illinois, USA
http://www.cancer.northwestern.edu/education/lynnage/cfm

ECCO 13—The European Cancer Conference
October 30–November 3, 2005
Paris, France
http://www.fecs.be

7th EUROPA DONNA Pan-European Conference
November 5–6, 2005
Rome, Italy
http://www.europadonna.org

17\(^{th}\) AACC-NCI-EORTC Molecular Targets and Cancer Therapeutics
November 14–18, 2005
Philadelphia, Pennsylvania, USA
http://www.eortc.be

San Antonio Breast Cancer Symposium
December 8–11, 2005
San Antonio, Texas, USA
http://www.sabcs.org

2006

Miami Breast Cancer Conference
February 22–25, 2006
Miami, Florida, USA
http://www.cancerconf.com

National Comprehensive Cancer Network (NCCN)
March 8–12, 2006
Hollywood, Florida, USA
http://www.nccn.org

Breast Diseases: Detection, Intervention and Therapy
March 13–16, 2006
Key Largo, Florida, USA
http://www.thebreastcourse.com

Society of Surgical Oncology
March 23–26, 2006
San Diego, California, USA
http://www.surgonc.org

American Association for Cancer Research
April 1–5, 2006
Washington, DC, USA
http://www.aacr.org

American Society of Breast Surgeons
April 5–9, 2006
Baltimore, Maryland, USA
http://www.breastsurgeons.org

American Society of Clinical Oncology
June 2–6, 2006
Atlanta, Georgia, USA
http://www.asco.org

Milan Breast Cancer Conference
June 21–23, 2006
Milan, Italy
http://www.breastmilan.com

European Society for Medical Oncology
September 29–October 3, 2006
Istanbul, Turkey
http://www.esmo.org
NOTICE TO MEMBERS: BIG and TRANSBIG Meetings

The next BIG/TRANSBIG meetings will take place as follows:

- **During ECCO 13, Paris**
  - TRANSBIG meetings Saturday, October 29, 2005 (for consortium members, by invitation)
  - BIG meeting Sunday, October 30, 2005, 9:00–14:30* (for BIG members)
  - *Please note earlier than usual starting time!

- **During EBCC-5, Nice**
  - TRANSBIG meetings Monday, March 20, 2006 (for consortium members, by invitation, details TBA)
  - BIG meeting Tuesday, March 21, 2006 (for BIG members, details TBA)

---

**Seventh EUROPADONNA**  
Pan-European Conference

European Breast Cancer Advocacy: Joining Voices-Meeting Needs

Keynote Speaker Commissioner Markos Kyprianou  
European Commissioner for Health and Consumer Protection

Rome, Italy  
November 5 and 6, 2005

---

For further information please contact:  
EUROPADONNA—The European Breast Cancer Coalition  
Via Previati 12, 20149 Milan, Italy  
Tel: +39 02 8907 9660  
Fax: +39 02 8907 9664  
E-mail: eevents@mclink.it  
www.europadonna.org  
(Member of Cancerworld)

---

We are grateful to the following companies for their contributions to the Secretariat in the form of unrestricted educational grants to support our communications activities other than this newsletter, which is supported by Schering-Plough: AstraZeneca, Amgen, Bayer, Eli Lilly, F. Hoffmann-La Roche, and OSI Pharmaceuticals.
Have you discovered Breast Cancer Online?
BCO provides a FREE electronic source of peer-reviewed data and your gateway to breast cancer research on the internet.

An essential resource
Breast Cancer Online is dedicated to the promotion and dissemination of the latest information, from core basic knowledge to state-of-the-art research. The content of the website is invited and reviewed by an independent international editorial board of experts from a multi-disciplinary perspective. Breast Cancer Online is intended for healthcare professionals with an interest in breast cancer research, treatment and care.

Featuring
- Focus On – providing timely reviews of topical or controversial subject areas
- Expert Opinion – discussion and analysis of interesting clinical cases by leading international experts
- Case Studies – notable real examples from clinical practice
- Journals Club
- Journals Watch
- Email content alerts
- Conference reports and calendar

To benefit from what Breast Cancer Online has to offer, register for free at www.bco.org