

THE INTERGROUP EXEMESTANE STUDY (IES): A MODEL FOR COLLABORATION

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ABSTRACT

Since Bradford Hill's first randomised trial in the 1940s, the conduct of clinical trials has changed greatly. Trials are now often multi-national, involve the collaboration of many academic groups and increasingly have pharmaceutical partners.

The IES is an excellent model for academia-industry collaboration. It has a unique administrative structure which has been adopted in subsequent trials. Although sponsored by industry, the IES was developed and is run by an academic group, the International Collaborative Cancer Group (ICCG), an international collaboration through a steering committee composed of members from the academic breast cancer groups involved.

The trial is run under the auspices of the Breast International Group - a consortium of breast cancer cooperative groups - which serves as a forum for introducing new trials and encouraging collaboration between its member groups.

The IES has a Coordinating Data Centre (CDC) to oversee the overall conduct of the trial, ensure consistent and accurate data, perform interim and final analyses and be responsible for liaison between the cooperative groups. Each group (LDC) is responsible for the day-to-day conduct of the trial in their hospitals and randomisation of patients. All data is monitored at the hospital before being sent to the LDC. The LDC acts as a 'mailbox' or performs local data management. All CRFs are forwarded to the CDC for entry to the central study database.

An Independent Data Monitoring Committee (IDMC), independent of the trial organisers and the pharmaceutical sponsor and their representatives, was established at the outset of the trial. The sponsor has no access to trial data until after the main efficacy analysis is performed.

This multi-level organisational approach (hospital ↔ LDC ↔ CDC) has proved highly successful for the IES. It allows large numbers of patients to be recruited within international trials while still maintaining the independence of individual breast cancer groups.

INTRODUCTION

The IES is a large international, randomised double blind trial and is a collaboration between the International Collaborative Cancer Group (part of Imperial College London), the Institute of Cancer Research (Sutton), the Breast International Group and Pharmacia (Milan). The trial opened in February 1998 and closed in February 2003 following the accrual of 4743 patients. This academic-led trial will be used for registration purposes.

ICCG

The International Collaborative Cancer Group (ICCG) is a European collaborative trials group which represents a successful partnership with the pharmaceutical industry. The ICCG was initiated 22 years ago and receives grant funding from industry to run trials in breast and gastric cancer. The ICCG Data Centre works in close collaboration with the Clinical Trials and Statistics Unit at the Institute of Cancer Research (ICR-CTSU), Sutton. The ICR-CTSU conducts the statistical analyses for all ICCG studies and also provides database and additional data management support.

BIG – THE INTERGROUP MECHANISM

It was agreed that the Intergroup Exemestane Study would run under the Breast International Group (BIG) umbrella. BIG, initially founded in 1996, functions essentially as an intergroup mechanism for its members, which are well established clinical research groups based worldwide. The primary role of BIG is to:

- facilitate and accelerate the initiation and progress of large breast cancer trials by increasing interaction and cooperation between its member groups
- draw on combined resources and reduce wasteful duplication of efforts
- permit the conduct of trials which one group on its own would not be able to run in a reasonable time period

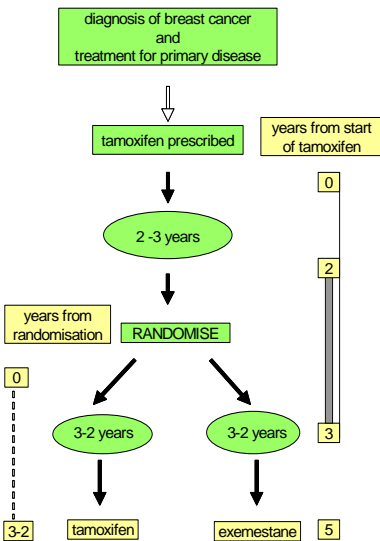
AIMS

The study rationale is to prevent or circumvent acquired tamoxifen resistance by means of a sequential approach to adjuvant endocrine therapy by comparing exemestane with further tamoxifen in postmenopausal women treated with 2 - 3 years tamoxifen.

STUDY DESIGN

ER+/unknown, postmenopausal patients disease-free after 2-3 years of tamoxifen were randomised to continue tamoxifen (20mg/day po) or switch to exemestane (25mg/day po) for a further 3-2 years (total 5 years) adjuvant endocrine therapy.

The IES aims to detect a 3.6% difference in (conditional) Relapse Free Survival (RFS) at 6 years.



ORGANISATION

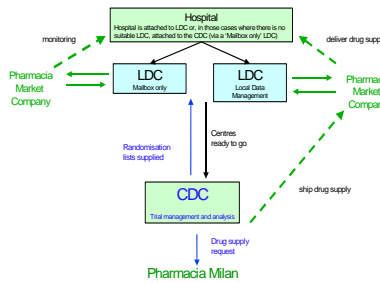
The overall conduct of the trial is overseen by a Coordinating Data Centre (CDC) which is responsible for the conduct, central data management and analysis of the trial and is housed at ICCG headquarters in London.

As the name suggests, the study is a collaboration between cooperative trials groups. Each group is responsible for the day-to-day conduct of the trial at their collaborating hospitals via the group's local data centre (LDC). Twenty cooperative groups covering 37 countries participated in the study. At the outset, each LDC chose its level of data management responsibilities (see box – Trial Management Options). This allowed flexibility for group participation whilst maintaining an identity for the collaborating regional or national groups. The centre initiation and data flow processes are shown opposite.

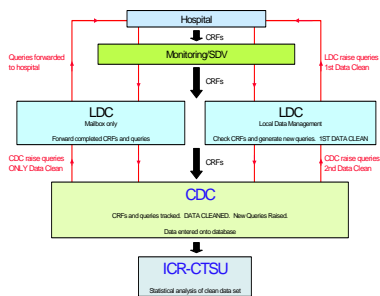
An Intergroup Steering Committee was set up with two representatives from each participating cooperative group (the local clinical study representative and the senior data manager or statistician involved from the LDC), plus the study statistician and a representative from the pharmaceutical sponsor.

An Independent Data Monitoring Committee (IDMC) was established at the outset of the trial, independent of the trial organisers and the pharmaceutical sponsor and their representatives.

TRIAL LOGISTICS

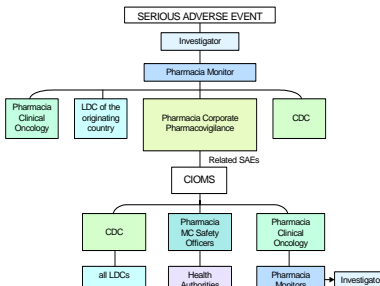


CRF AND QUERY FLOW



Monitoring of the study is carried out by LDCs or Pharmacia monitors

SAE FLOW



TRIAL MANAGEMENT OPTIONS



Option A – LDC as Mailbox

- Obtain any missing data and resolve queries with hospital before sending to CDC
- Forward top copy of all CRF pages received to CDC
- Send corrections back to CDC
- Receive report of monitoring
- Resolve problems arising from monitoring with investigators
- Receive reports of SAEs from hospital (via monitor)

Option B – LDC as Local Data Management

- Obtain any missing data and resolve queries with hospital before data entry of CRF
- Enter CRFs on to database in order to perform data clean and check, ie complete data management. Flag problems
- Forward top copy of all CRF pages – after full clean – to CDC
- Forward queries received from CDC to hospitals
- Send corrections back to CDC
- Receive report following monitoring
- Resolve problems arising from monitoring with investigators
- Receive reports of SAEs from hospital (via monitor)

DATA ANALYSIS

All data are entered on to a central database, held at ICR-CTSU, by the CDC. All analyses of the main study and sub-protocol data are performed by the trial statistician independent of the pharmaceutical sponsor.

As the trial will be used for regulatory purposes, collaboration with the sponsor in terms of database format and support for coding (eg of concomitant medications) has been necessary, informative and useful. Now that recruitment has closed, and with approval from the Steering Committee, the sponsor will receive a 33% random subset of the data (and annual updates) blinded to treatment allocation. This will allow them to prepare the format of the final study report for regulatory submission. However, no additional unblinded data will be released to the sponsor until the database had been frozen and the principal efficacy analysis completed and submitted to the Steering Committee. Reports for publication and regulatory submission will be based on, and be consistent with, the same data snapshots and analyses.

ACCRUAL BY COUNTRY



GROUPS PARTICIPATING

- Argentine Breast Cancer Group (148)
 - Australia New Zealand Breast Cancer Trials Group (70)
 - Central and Eastern European Oncology Group (912)
 - Danish Breast Cancer Group (136)
 - European Organisation for Research & Treatment of Cancer (432)
 - Fédération Nationale des Centres de Lutte Contre le Cancer (398)
 - German Exemestane Adjuvant Group (185)
 - Grupo Espanol de Investigación del Cáncer de Mama (254)
 - Gruppo Oncologico Italiano di Ricerca Clinica (112)
 - Gruppo Oncologico Nord Ovest (199)
 - International Breast Cancer Study Group (183)
 - International Collaborative Cancer Group (576)
 - Israeli Clinical Oncology Group (62)
 - Italian Trials in Medical Oncology (179)
 - Nationaal Borstkankeroverleg Nederland (via EORTC)
 - North West England Cancer Group (33)
 - Norwegian Breast Cancer Group (126)
 - Swedish Breast Cancer Group (163)
 - US Oncology (357)
 - Wales Cancer Trials Network (58)
 - Yorkshire Breast Group (160)
- Number of patients entered is given in parentheses

SUMMARY

This study demonstrates that independently managed trials involving multiple collaborative groups and a company sponsor can be effective, fast-recruiting and appropriate for the adjuvant setting.

ACKNOWLEDGMENTS

To Graeme Kerson & Lynne Booth (CDC) for preparing the poster
To all investigators and study staff worldwide
To all the women who have taken part in the study

ASSOCIATED STUDIES

There are three sub-protocols linked with the main study.

Participation in the sub-protocols was determined at an LDC level thus allowing some flexibility dependent on each group's interests.

QUALITY OF LIFE (QOL) 581 patients
The FACT-ES questionnaire has been developed to measure QOL in patients receiving endocrine therapy and so should be sensitive to QOL changes between the two treatments in women in this trial. The study is coordinated at the Cancer Research UK Psychosocial Oncology Unit, University of Sussex, Brighton, UK. Questionnaires are completed by the women themselves and are sent either to the national QOL coordinator and then to the CDC, or directly to the data centre.

BONE 206 patients
The study will assess and quantify the changes in bone mineral density (BMD) in the two arms of the study. DXA scans (the method by which BMD is measured) are evaluated at the Bone Density Unit, Charing Cross Hospital, London. Blood and urine samples are sent to the central laboratory at Hammersmith Hospital, London, for analysis of bone markers.

ENDOMETRIUM 219 patients
Ultrasound examination, a non-invasive imaging technique, is used to measure endometrial thickness. The proportion of women with an endometrial thickness ≥ 5 mm after two years of randomised treatment is compared. Data are collected and recorded using the same procedure adopted by the main study.