



IBIS-II (DCIS)

PROTOCOL

An international multi-centre study
of
tamoxifen vs anastrozole
in
postmenopausal women
with
Ductal Carcinoma in Situ (DCIS)

Approved



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Introduction

IBIS-II (DCIS) is designed to continue the work started in IBIS-I in determining whether a chemopreventive strategy towards breast cancer is beneficial. IBIS-I was set up to investigate the use of tamoxifen as a preventive agent for women with moderate to increased risk of getting breast cancer. IBIS-II (DCIS) is a randomised double blind control trial which will compare tamoxifen versus anastrozole in women with locally excised ER or PgR positive Ductal Carcinoma In-Situ (ER or PgR+ve DCIS).

This study will be run in accordance with the ICH GCP Guidelines, the principles of which have their origins in the Declaration of Helsinki 2000.

Cancer Research UK is supporting this research study and Queen Mary, University of London are the sponsors.

1. Aims

1.1. Primary

- 1) To determine if anastrozole is at least as effective as tamoxifen in local control and prevention of contralateral disease in women with locally excised ER or PgR positive DCIS.
- 2) To compare side effect profiles of tamoxifen and anastrozole.

1.2. Secondary

- 1) To compare the effectiveness of tamoxifen and anastrozole according to the receptor status of the primary or recurrent cancer.
- 2) To examine the rate of breast cancer recurrence and new contralateral tumours after cessation of tamoxifen or anastrozole.
- 3) To examine the effect of tamoxifen vs anastrozole on breast cancer mortality.
- 4) To examine the effect of tamoxifen and anastrozole on other cancers, cardiovascular disease, fracture rates, and non-breast cancer deaths.

- 5) To examine tolerability and acceptability of side effects experienced by women on the study.

2. Background

DCIS was once a rare diagnosis, but it has become increasingly common following the advent of mammographic screening. In the UK, DCIS currently comprises 20% of screen detected cancer, and similar figures are found elsewhere. Thus, the appropriate treatment for this disease has now become an increasingly important issue. It is generally agreed that adequate local treatment comprises either mastectomy or local excision with clear margins (with or without radiotherapy). For localised DCIS many clinicians consider mastectomy to be over-treatment and a focus of current research is the need for additional treatment after complete local excision. Radiotherapy has been shown to reduce local recurrence rates by 60-70% (Fisher. et al., (1999), EORTC, (2000), UKCCCR DCIS Working Party, (2001)), but there is still uncertainty as to which group of patients require this rather intensive treatment. Adjuvant endocrine therapy has also been advocated, and there are two trials which have addressed this issue. The North American NSABP B-24 trial looked at the value of giving tamoxifen to women who had received radiotherapy. A highly significant 37% reduction in recurrence rate was found. (Fisher, *et al.*, 1999). However, the recently completed UK trial has not been so positive, reporting a non-significant 17% reduction in recurrence (UKCCCR DCIS Working Party, 2001). The clear benefit of tamoxifen in the adjuvant studies, even for early stage I disease also provides strong support for an effect of hormonal therapy in DCIS. These two trials will continue to explore the value of tamoxifen with further follow-up, and the focus of the current trial will be to evaluate whether the aromatase inhibitor anastrozole has advantages over tamoxifen, either in terms of reduced recurrence rates or lower side effects.

Aromatase inhibitors are a class of compounds that act systemically to inhibit oestrogen synthesis in tissues. These compounds prevent oestrogen biosynthesis by inhibiting the enzyme aromatase, which catalyses the conversion of adrenal androgens (androstenedione and testosterone) to oestrogens (oestrone and oestradiol). There has therefore been interest in developing these compounds as potential therapies for hormone responsive breast cancer in postmenopausal women.

In postmenopausal women, oestradiol is produced primarily from the conversion of androstenedione to oestrone through the aromatase enzyme complex in peripheral tissues. Oestrone is subsequently converted to oestradiol. Reducing circulating oestradiol levels, either by the use of gonadotrophin releasing hormone (GnRH) agonists in premenopausal women (Rutqvist 1999; Jakesz, *et al.*, 1999) or by the use of aromatase inhibitors in postmenopausal

women (Nabholtz *et al.*, 2000), has been shown to produce a beneficial effect in women with breast cancer.

Aminoglutethimide was the first aromatase inhibitor to be approved for the treatment of breast cancer and has proven efficacy in postmenopausal women with advanced breast cancer (Stuart-Harris *et al.*, 1984). Wider use of the drug has been limited by its lack of specificity, resulting in a requirement for concomitant administration of corticosteroids, and the occurrence of troublesome side effects (Wells *et al.*, 1978). Consequently, research has been focused on the development of aromatase inhibitors with greater specificity and a better tolerability profile.

The new third generation aromatase inhibitors have shown good efficacy in advanced breast cancer and have a very low toxicity profile. They offer another approach to local control, prevention of recurrence and the prevention of primary breast cancers, which may be superior and/or complimentary to the use of SERMs.

Anastrozole is a potent new non-steroidal aromatase inhibitor which is highly selective, well tolerated and is effective in treating advanced breast cancer (Buzdar *et al.*, 1997; Jonat *et al.*, 1996; Plourde *et al.*, 1995; Nabholtz *et al.*, 2000). In postmenopausal women, a daily dose of 1 mg anastrozole produces oestradiol suppression of greater than 80% using a highly sensitive assay (Geisler *et al.*, 1996). Anastrozole does not possess progestogenic, androgenic or oestrogenic activity.

In controlled clinical trials in advanced, tamoxifen-resistant breast cancer, anastrozole at the daily dose of 1 mg has demonstrated superior clinical efficacy to a standard second line hormonal treatment with megestrol acetate (Buzdar *et al.*, 1998). Recent trials of anastrozole as first line treatment in advanced breast cancer suggest that it is as good as and possibly superior to tamoxifen. In particular, Nabholtz *et al.*, (2000) have reported that anastrozole may be more effective than tamoxifen as first line treatment for ER-positive advanced breast cancer (hazard ratio 0.69, $P = 0.005$ for time to progression in one study with mostly ER-positive tumours only; no difference overall in a second study (HR = 1.0), but HR = 0.87 in ER-positive patients in that study). A recent update of the combined data (Buzdar, *et al.* 2000) showed that time to progression was significantly increased with anastrozole in patients with receptor positive tumours (median 10.7 vs. 6.4 months, $P = 0.02$). Toxicity has generally been similar or lower (especially for thromboembolic disease and vaginal bleeding) in the anastrozole arm.

A very large trial (ATAC) is currently evaluating the role of anastrozole both alone and in combination with tamoxifen compared to tamoxifen in the adjuvant setting for early breast cancer. This trial has recruited 9366 patients and more than 1000 recurrences or deaths have now been recorded. After a median follow-up of 33 months, the initial result has been publically announced (ATAC Trialists, 2002). Significantly fewer recurrences have been reported on the anastrozole arm compared to tamoxifen (HR=0.83, $p=0.013$). New contralateral tumours were

also reduced by 58% ($P= 0.007$) compared to tamoxifen. To date there are no significant differences in distant recurrence and a survival analysis has not been conducted. The side effect profile is generally favourable, with fewer endometrial cancers, thromboembolic events, strokes and hot flushes than tamoxifen (Table 1, Section 4.2). However, there are significant increases in musculo-skeletal disorders (primarily arthralgia) and fractures in the anastrozole group when compared with the tamoxifen group (Table 1). Thus there is a strong case for comparing anastrozole to tamoxifen in ER or PgR +ve DCIS.

As of April 2002, the total exposure to anastrozole exceeded 550,000 patients-years (personal communication, T. Sahmoud, AstraZeneca) and this is increasing rapidly. A review of the clinical trial safety database did not reveal evidence of clinically significant interaction in patients treated with anastrozole who also received other commonly prescribed drugs.

3. Study Design

3.1. Outline

A multicentre, randomised, double-blind, double-dummy clinical trial of 4,000 postmenopausal women aged between 40 and 70 years with ER or PgR+ve DCIS who have received adequate local treatment will be conducted. A blood sample will be taken for analysis of biochemical and other risk factors for breast cancer and potential side-effects.

A parallel trial of 6,000 women at increased risk of breast cancer will also be conducted (see IBIS-II (Prevention) protocol).

3.2. Dose and Duration

Women will be randomised in a 2-arm design to receive one of the following:

1. Tamoxifen 20mg + Anastrozole placebo
2. Anastrozole 1mg + Tamoxifen placebo

Randomisation will be stratified by major (hub) centre. Randomised blocks will be used to maintain balance. Randomisation will be performed centrally by electronic contact with the main trials centre and will be available at all times. Provisions for back-up randomisation in national centres will also be provided. All treatment will be on a daily basis for 5 years and all women will take 2 tablets/day. One will contain tamoxifen or placebo. The second tablet will contain either anastrozole or placebo. Tablets will be supplied in numbered light-proof

containers containing a 6 month supply. Each container will have extra tablets to allow for some delay in the next appointment. **Physicians and nurses must attempt to determine that compliance is likely to be good (of a high standard) before randomising subjects.**

3.3. Participating Centres and Recruitment

All centres will randomise through the Central Office in London, primarily by remote FTP (file transfer protocol, internet standard). Back-up systems will be provided for randomising by fax and failing that, by telephone or e-mail. The remote randomisation will be part of the standard trial software distributed to all centres for the data management of the trial.

3.3.1. UK

Recruitment will be based at regional centres. Regional centres will enter patients at their own hospital and also serve as a local co-ordinating (hub) centre for satellite centres in nearby hospitals throughout the region. Each centre will be expected to recruit an agreed number of new participants per year to reach their target over 4 years.

3.3.2. Non-UK

All non-UK centres are responsible for collection and management for blood samples and other specimens obtained from their participants. Data and specimens will be transferred to the Central Office at regular intervals.

Where possible other international centres will be managed through existing national or international trial groups.

3.4. Eligibility

3.4.1. Inclusion Criteria

- a) All women must be postmenopausal and between the ages of 40-70. Postmenopausal status is defined as meeting one or more of the following criteria:
1. over the age of 60
 2. bilateral oophorectomy
 3. aged ≤ 60 with a uterus and amenorrhoea for at least 12 months
 4. aged ≤ 60 without a uterus and with FSH >30 IU/L

- b) Locally excised DCIS diagnosed within the last 6 months (includes Paget's disease with underlying DCIS) Oestrogen Receptor or Progesterone Receptor (ER or PgR) status of DCIS must be known and must be greater than 5% positive cells.
- c) A baseline bone mineral density scan within the last two years (DXA either of hip, lumbar spine or forearm) will be required for all women. A spinal x-ray to rule out low trauma vertebral fractures will also be required.
- d) Fully informed signed consent must have been obtained.
- e) Participants who took part in IBIS-I but have been off trial therapy for at least 5 years.

3.4.2. Entry Criteria

The trial is open to women with locally excised ER or PgR +ve DCIS diagnosed within the last six months in which there are tumour free margins of at least 1mm. Patients with a single focus of microinvasion (<1mm) are eligible to join IBIS-II. Radiotherapy may or may not be given or can be randomised as in the planned UK British Association of Surgical Oncology (BASO) DCIS-II trial. Depending on local practice, the hormone therapy can be started before, during, or after the course of radiotherapy. The DCIS-II trial will be integrated into the IBIS-II (DCIS) trial at certain centres in the UK and possibly elsewhere. Margin status and oestrogen or progesterone receptor status will be determined by the local pathologist, but slides will be required for central review. Tissue blocks (or 10 unstained slides, if blocks cannot be released) will be requested for additional marker studies. Slides and blocks will be returned promptly if required..

Women treated by mastectomy will not be eligible for this trial, but can enter the parallel IBIS-II (Prevention) trial to evaluate the role of these drugs in preventing contralateral breast cancer.

3.4.3. Exclusion Criteria

- a) Premenopausal women.
- b) Any previous diagnosis of breast cancer (including DCIS diagnosed >6 months ago)
- c) Any other previous cancer in the past 5 years (except non-melanoma skin cancer or in situ cancer of the cervix)
- d) Current treatment with anti-coagulants.

- e) Previous deep vein thrombosis or pulmonary embolus.
- f) Previous transient ischaemic attack (TIA) or cerebrovascular accident (CVA, stroke).
- g) Current or previous tamoxifen or raloxifene or other SERMs use for more than 6 months or participation in IBIS-I. However, women who took part in IBIS-I and have been off trial therapy for at least 5 years are eligible.
- h) Intention to continue to use oestrogen-based hormone replacement therapy (HRT).
- i) Women who have either had a prophylactic mastectomy or are planning to have this procedure.
- j) Any woman with unexplained postmenopausal bleeding.
- k) Evidence of osteoporosis or low trauma vertebral fractures within the spine. However, these women may be eligible if their T-score is more than minus four and they have no more than two low trauma vertebral fractures. In either case they must take bisphosphonate treatment and have regular DXA scans. The results of the scans must be provided to the trial, as for women in the IBIS-II Prevention bone sub-protocol. Women with T-scores of less than minus four or with more than two low trauma vertebral fractures are not eligible.
- l) Any severe concomitant disease that would, in the opinion of the investigator, place the woman at unusual risk or confound the results of the study.
- m) Life expectancy of less than 10 years or other medical condition which would significantly interfere with the ability to accept the chemopreventive treatments.
- n) Psychologically and physically unsuitable for five years anti-oestrogen therapy.
- o) Treatment with non-approved or experimental drug during the 6 months before randomisation.
- p) History of gluten intolerance.

Systemic oestrogen replacement therapy is not allowed whilst women are taking trial medication. If serious menopausal symptoms develop during treatment, the following approach should be adopted:

1. Non hormonal complementary therapies may have some beneficial effect and some women may achieve relief from dietary and lifestyle changes.
2. Non hormonal treatment of specific symptoms, eg venlafaxine may help with hot flushes. Senselle (a water based, non hormonal vaginal lubricant) may alleviate vaginal dryness. Following the report of the Million Women Study (Beral, 2003) progestagens or tibolone are contra-indicated for women at increased risk of breast cancer.
3. In cases of serious vaginal discomfort low dose oestrogen preparations may be used for as short a period as possible.
4. If the above are unsuccessful, trial medication can be reduced to alternate days. If symptoms persist, a treatment holiday can be tried next.
5. If unacceptable symptoms persist and oestrogen-based therapy is deemed necessary, then trial medication must be stopped. If, at a later stage, HRT is stopped, then trial medication can recommence.

Each of the above options must be clearly documented in the participants' records. Breaks from trial medication should be kept to a minimum, ideally no longer than 1 to 3 months.

4. Study Procedures

4.1. Investigations

4.1.1. Mammography

All women will have a physical examination and mammogram (and where necessary fine needle cytology or biopsy) to characterise the existing malignancy. The date and identification number of all mammograms should be recorded to facilitate access to mammograms for central review purposes. During the follow-up period mammography will be performed at intervals, which will be decided locally, or as considered necessary for clinical reasons. Mammography should be performed at least once every two years.

4.1.2. Bone Mineral Density (BMD)

A baseline DXA scan within the last two years will be required for all women prior to randomisation. This can be at any site, and use of portable DXA machines that examine the forearm are acceptable. Patients in the DCIS study are not eligible for the bone sub-protocol, but if osteoporotic must be monitored and treated as in the sub protocol.

4.1.3 Spinal Radiograph

A baseline radiological assessment must be carried out within two years prior to randomisation to rule out low trauma vertebral fractures. This requires two x-rays in one lateral dimension to view the thoracic and the lumbar vertebrae. These must be reported on by a qualified radiologist and the report must be available before randomisation takes place. If there are more than **TWO** low trauma vertebral fractures then the woman cannot take part in any of the IBIS-II protocols (The European Prospective Osteoporosis Study (Epos) Group, 2002).

4.2. Personal and Medical Details

A questionnaire giving height, weight, smoking habits, selected, clinically relevant medical history and risk factors for breast cancer must be completed for all women entering the study – entry Case Report Form (CRF).

Information on prescriptions and hospital visits (other than those directly associated with the study) will be recorded in order to facilitate an assessment of additional costs or savings to the health service related to long term use of tamoxifen or anastrozole. It is difficult to estimate what the outcome of this analysis will be at this stage, since the costs of diagnosing and treating some side effects (e.g. endometrial, bone or eye problems) may be more than offset by reductions in other areas (e.g. osteoporosis, fractures and heart disease).

4.3 Samples and Specimens

4.3.1. Blood samples

Women will have a sample of 14ml (2 x 5ml SST tubes and 1 x 4ml EDTA tube) venous blood samples taken at entry and 10 ml (2 x 5ml SST tubes only) will be taken at years 1 and 5 as clotted whole blood. 4 ml of the entry sample will be put into the EDTA tube provided and used to look for susceptibility genes to breast cancer or side effects. In the UK, both tubes will be posted immediately by first class postage in pre-addressed SARSTEDT t-box containers to Dr. William Richmond at the St. Mary's Hospital, London. All samples except the EDTA sample must be spun down locally before posting. Follow-up samples will be treated identically except that the EDTA tube will not be required. Bloods will be stored at -70°C and analysed retrospectively,

mostly on a case-control basis in an anonymous fashion. They will be used to evaluate biomarkers, which are potential but not yet established markers for risk of disease or response to the preventive therapies under study. The follow-up blood samples will also be used to monitor compliance in a sample of women. The blood samples will remain the property of the Steering Group.

Arrangements for blood samples taken in other countries will be made in collaboration with the IBIS Co-ordinating Centre on an individual basis, with frozen aliquots being sent in dry ice to London for long-term storage on a regular basis.

4.3.2. Pathology specimens

A set of representative diagnostic H&E stained slides plus the original hormone receptor assay slides (ER and/or PgR) will be required from all patients for central review. Paraffin blocks containing representative areas of the tumour will also be requested. The latter will be used to make additional slides and tissue arrays, and will be returned to the sender. If possible, the pathologist should be made aware of the woman's involvement in the IBIS-II Study before blocks are taken. It may then be possible to make extra blocks and slides specifically for study purposes. If blocks are not available, 10 unstained sections on uncoated slides should be provided. A standard DCIS Pathology Entry Form must be completed for each specimen and this is included in the case report forms. In addition, a copy of the original pathology reports (and a copy of the UK Sloane form, where available) must be provided. Diagnostic slides and paraffin blocks will be requested for all breast, endometrial, or ovarian cancers developing after trial entry. These samples will be used for central pathology review and marker studies, and will remain the property of the Steering Group, who will be responsible for deciding how they will be used in any further projects.

4.4. Sub Studies

Measurements of changes in hormone levels, lipid profiles, bone biomarkers, and endometrial biopsies will be made in selected centres and will be considered as separate studies and are not addressed in this protocol. Data collection will be kept at a minimum and only items that are essential to analyse the specific endpoints listed below will be collected. All protocols for special studies will be submitted to the Steering Committee for information and co-ordination. These studies will require appropriate Ethics Committee approval.

4.5. Management of Trial Participants

4.5.1. Routine Follow-up

Women will be seen in clinic at six months and one year in their first year of participation. Then they may be seen annually with an option to attend for a six monthly visit as well. All women may also be contacted by their Local Coordinator every six months to offer ongoing support and information as necessary during the five years of treatment but no data is required for the study at these contacts. Advice on maintaining healthy bones (e.g. calcium and vitamin D supplementation, sunlight and weight bearing exercise) will be offered to all women in the trial. Treatment with bisphosphonates should be considered where necessary. The use of raloxifene or any other SERM, or HRT for osteoporosis or any other reason is not permitted in this trial. Interested general practitioners (GPs), and those within the vicinity of a centre, will be sent the study protocol and information leaflets, as these GPs will be very important both for recruitment and for support during the study, which should help with compliance. Blood samples (10ml) to document changes in biomarkers and to monitor compliance will be taken at year 1 and year 5. Mammograms will be taken at intervals, to be decided locally, but at least every two years. These will be reviewed centrally on a subset to examine the effects of treatment on mammographic opacities. After 5 years of treatment, women should receive an annual questionnaire (either by post or at clinic) for another 5 years. In the UK, women will be flagged centrally through the National Registry at Southport, the Scottish Registry or the Northern Ireland Registry for cancer incidence and mortality. In other countries similar existing tracking systems will be used to follow up women.

4.5.2. Compliance

If women are concerned about a symptom potentially related to trial medication, it is preferable to consider trying a dose reduction, i.e. alternate days, or offer a 'treatment holiday' rather than to stop treatment altogether. Full treatment can be restarted after an appropriate interval (usually 1-3 months) or a decision about withdrawal can be made subsequently if symptoms persist. Treatment holidays can also be used in other special circumstances, but should always be documented on the follow-up form, as should changes in daily dose.

4.5.3. Treatment Cessation

Treatment should be stopped before any major operation.

Adherence to treatment protocol will cease if any of the following circumstances arise:

- i) the woman develops another breast cancer (including either recurrent or new DCIS)
- ii) her T-score drops below minus four

- iii) she is found to have a new low trauma vertebral fracture
- iv) she develops a deep vein thrombosis, pulmonary embolism, transient ischaemic attack, cerebrovascular accident or other symptom or condition related to serious thromboembolic disease.

The trial medication will be stopped and the woman should be referred for treatment according to local practice. Should a woman develop any concurrent condition, for example heart disease, during the study, it would not be considered necessary for her to leave the study. However, as with any illnesses that develop during the woman's participation in the study, the decision about continuing will rest with the clinician involved, the woman herself and her general practitioner.

4.5.4. All Adverse Events

4.5.4.1. Adverse Events (AE)

An adverse event is defined as the development of a new, undesirable medical condition or the deterioration of a pre-existing condition following or during exposure to a medicine **whether or not considered causally related to the product**. A medical condition can be a symptom (such as nausea or chest pain) a sign (such as rash or enlarged liver) or an abnormal result of an investigation (including blood tests, x-rays or scans or various types). In clinical studies, an AE can include an undesirable medical condition occurring at any time, even if no study treatment has been administered.

All adverse events must be recorded and reported if they begin at any time whilst the patient is receiving the randomised treatment and during 30 days after treatment withdrawal. The development of a new non breast primary cancer, which has been identified after inclusion into the clinical trial should be regarded as an adverse event. Local recurrence of ER or PgR +ve DCIS will be regarded as a lack of efficacy. This will be recorded as a specific endpoint on the CRF and does not need to be reported as an adverse event.

This will be reported via the relevant follow-up CRF.

4.5.4.2. Serious Adverse Events (SAE)

A serious adverse event is an event that fulfils one or more of the following criteria:

- is fatal
- is life-threatening
- requires in-patient hospitalisation or prolonging hospitalisation
- results in disability or incapacity

- or is an important medical event that may require medical intervention to prevent permanent impairment or damage.

The causality of SAEs (ie, their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant CRF must answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the drug?” If the answer to this question is yes, the SAE will be classified as a Serious Adverse Reaction (SAR) – See Section 4.5.4.3

All SAEs will be reported to the IBIS Central Coordinating Centre within 24 hours.

All SAEs, including those that are ongoing at the end of the follow-up period, will be followed to resolution unless, in the investigator’s opinion, the condition is unlikely to resolve due to the patient’s underlying disease.

4.5.4.3 Suspected Unexpected Serious Adverse Reaction (SUSAR) and Serious, Suspected Adverse Reactions (SSAR’s)

Local centre investigators are responsible for assessing seriousness and relatedness of an adverse reaction.

All SAEs (including SARs) will be reported to the IBIS Central Coordinating Centre within 24 hours.

It will be the responsibility of AstraZeneca to confirm whether the SAR is a Suspected Unexpected Serious Adverse Reaction (SUSAR) or a Serious Suspected Adverse Reaction (SSAR) and to forward any SUSARs to the regulatory authority. (Appendix 4)

4.5.4.4. Recording of adverse events

All adverse events will be recorded in the electronic SAE CRF provided, providing the following information as appropriate:

Description of event; dates and times of onset and resolution; event intensity; seriousness; outcome; causality; any action taken (e.g. treatment, diagnostic tests). It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in the previous 4.5.4 sections. An AE of severe intensity need not necessarily be considered serious. For example, nausea, which persists for several hours, may be considered severe nausea, but not a SAE. On the other hand, a stroke resulting in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Additional details on action taken, including diagnostic procedures, will be recorded for any patients with vaginal bleeding or discharge. Any patients who report abnormal vaginal bleeding, or discharge or pelvic pain or pressure should be promptly investigated. It is not mandatory that the code is broken in such cases, but this may be done if requested by the treating physician, when necessary for further treatment

4.5.4.5 Reporting of serious adverse events

Investigators and other site personnel must inform London IBIS Central Office of any SAE that occurs in the course of the study immediately (within 24 hours) of when he or she becomes aware of it.

The electronic SAE CRF will be sent to the IBIS Central Coordinating Centre within 24 hours and by selecting the "Talk-to-CR-UK" option on the IBIS-II program. A hard copy of the SAE CRF should also be printed, signed by the local principal investigator and faxed to the IBIS Central Coordinating Centre as soon as he or she becomes available (Fax: +44 (0)20 7014 0248)

Follow-up information on SAEs must also be reported by the investigator within the same time frame.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided within 1 day as described above.

5. Toxicity and Hazards

5.1. Tamoxifen

Tamoxifen has been used as first line adjuvant treatment for breast cancer for over 20 years. Tamoxifen is a comparatively well tolerated drug with minimal reported side effects (Fallowfield *et al.*, 2001). In placebo-controlled trials in well women (Powles *et al.*, 1990; Fisher *et al.*, 1998), it was found that non-specific side effects such as nausea, vomiting and headaches were no more common for tamoxifen than for the placebo group. Menopausal hot flushes, vaginal discharges and vaginal dryness were more common for tamoxifen than for placebo but these have had a minor effect on compliance. Intolerance occurs rarely and the relevant side effects usually resolve rapidly on cessation of medication. Other side effects which have been reported to the manufacturer include light-headedness, skin rash, fluid retention, thrombocytopaenia, gastrointestinal disturbances, alopecia, visual problems (Kaiser-Kupfer *et al.*, 1978; Bentley *et al.*, 1992), vaginal bleeding and in premenopausal women cystic ovarian swellings and suppression of menstruation.

As all women will be postmenopausal, pregnancy risk will not be an issue in this trial.

Except for endometrial cancer, no other cancer appears to be associated with tamoxifen treatment (EBCTCG, 1998; Jackson *et al.*, 1991). Endometrial cancer appears to be increased to about 2-3 times the background rate from about 4/10000 per year to 8-12/10000 per year. There appears to be little excess risk in premenopausal women, but an approximately 4-fold risk has been observed in postmenopausal women (Fisher *et al.*, 1998). These excess cancers generally have a good prognosis and most are FIGO grade 1 stage 1. However, an excess of high grade tumours has been reported. (Bergman, *et al.*, 2000), but they were very rare and mostly associated with more than 5 years of tamoxifen use and higher daily doses (30 or 40 mg).

Thromboembolic complications also are increased about 3-fold in increased risk women taking tamoxifen (Fisher *et al.*, 1998). In some cases a fatal pulmonary embolism has occurred, but the absolute excess risk is very small, being 6 cases of DVT and 4.5 cases of pulmonary emboli per 10,000 women-years of follow-up.

The full list of adverse reactions to tamoxifen is available as a separate document. (Astra Zeneca Core Data sheet).

5.2. Anastrozole

Anastrozole has been used in the treatment of breast cancer for 7 years and is generally well tolerated. Reported adverse events have usually been mild to moderate with only few withdrawals from treatment due to undesirable events. The pharmacological action of anastrozole may give rise to certain expected effects. These include hot flushes, vaginal dryness and hair thinning. Anastrozole may also be associated with gastrointestinal disturbances (anorexia, nausea, vomiting and diarrhoea), asthenia, arthralgia, somnolence, headache or rash.

Anastrozole has been used in advanced breast cancer and has been found to be at least as effective as tamoxifen, but with fewer side effects (Bonnetterre *et al.*, 2001) (see Table 1). Until recently its use as an adjuvant in early breast cancer has been restricted to clinical trials, but it has now been licensed for use in the adjuvant setting in several countries.

Results from an adjuvant trial (ATAC) (ATAC Trialists, 2002) enrolling over 9000 postmenopausal patients indicate that anastrozole is more effective in reducing early recurrences than tamoxifen (P=0.013). At the time of this report, the median follow-up was 33.3

months and median duration of treatment was 30.7 months. The side effect profile is also generally more favourable (Table 1), with fewer endometrial cancers, thromboembolic events, strokes, and hot flushes. However, musculoskeletal symptoms (mostly arthralgia) and fractures of osteoporotic sites and other sites are increased. It is not yet clear the extent of bone loss associated with anastrozole. Also, no studies to date have been conducted to investigate concomitant use of vitamin D and calcium or bisphosphonate in combination with anastrozole. Because of the profound reduction of circulating oestrogen levels in women taking anastrozole, effective management of potential bone loss is likely to be important. Detailed bone density studies are currently underway in the adjuvant trials, and will also be undertaken within the prevention stratum of this trial. A separate bone sub-protocol will address these issues in the prevention stratum.

Table 1. Pre-specified adverse events in the ATAC adjuvant trial. (%)

	Anastrozole (N= 3125)	Tamoxifen (N= 3116)	Combination (N=3125)
Hot flushes	34.3	39.7	40.2
Nausea and vomiting	10.5	10.2	11.7
Fatigue/Tiredness (Asthenia)	15.7	15.1	14.0
Mood disturbances	15.5	15.2	15.6
Musculo-skeletal disorders	27.8	21.2	22.1
Vaginal bleeding	4.5	8.1	7.7
Vaginal discharge	2.8	11.4	11.4
Endometrial cancer ¹	0.1	0.5	0.2
Fractures	5.8	3.7	4.6
Fractures of spine/hip/wrist	2.2	1.4	1.6
Ischaemic cardiovascular disease	2.5	1.9	2.2
Ischaemic cerebrovascular event	1.0	2.1	1.6
Venous thromboembolic events	2.1	3.5	4.0
Deep venous thromboembolic events	1.0	1.7	2.0
Cataracts	3.5	3.8	3.4

¹ Excluding patients with hysterectomy at baseline

Anastrozole is not recommended for use in premenopausal women as safety and efficacy have not been established in this group of women. Anastrozole has not been investigated in patients

with severe hepatic or severe renal impairment, but women with these conditions will not be eligible for the trial. The potential risk/benefit to such patients should be carefully considered before administration of anastrozole.

Antipyrine, warfarin and cimetidine clinical interaction studies indicate that the co-administration of anastrozole with other drugs is unlikely to result in clinically significant drug interactions mediated by cytochrome P450.

Hepatic changes (elevated gamma-GT or less commonly alkaline phosphatase) have been reported in patients with advanced breast cancer, many of whom had liver and/or bone metastases. A causal relationship for these changes has not been established. Slight increases in total cholesterol have also been observed in clinical trials with anastrozole.

Daily doses of anastrozole up to 10 mg do not have any effect on cortisol or aldosterone secretion, measured before or after standard ACTH challenge testing. Corticoid supplements are therefore not needed.

Events of Carpal Tunnel Syndrome have been reported in patients receiving Arimidex treatment in clinical trials in greater numbers than those receiving treatment with tamoxifen. However, the majority of these events occurred in patients with identifiable risk factors for the development of the condition.

In the ATAC trial, ischaemic cardiovascular events were reported more frequently in patients treated with Arimidex compared to those treated with tamoxifen, although the difference was not statistically significant. The observed difference was mainly due to more reports of angina pectoris and was associated with a sub-group of patients with pre-existing ischaemic heart disease.

The full list of adverse reactions to anastrozole is available as a separate document. (Astra Zeneca Core Data sheet)

6. Analysis of Data and Statistical Considerations

6.1. Randomisation

Analysis will be based on randomised treatment option (intent to treat or ITT). For this reason it is important to attempt to ensure good compliance before randomisation.

Randomisation will be stratified by individual major (hub) centre only. The randomisation will not be stratified for the other risk factors, but they will be used to achieve retrospective stratification at the time of analysis. Factors that will be examined in the primary analysis of ipsilateral events are, use of radiotherapy, extent of margins and grade.

6.2. Endpoints

The primary endpoint is the development of histologically confirmed breast cancer, both invasive and non-invasive (i.e. including new or recurrent DCIS). These will be separately categorised as local recurrence (all ipsilateral disease), distant recurrence or new contralateral tumour but the primary analysis will be based on all of them.

A concurrent DCIS trial is being planned in North America and it is anticipated that a separate main analysis for this stratum will be performed earlier to facilitate a pre-planned meta-analysis with that study.

Adherence to treatment protocol will cease if a woman develops new or recurrent breast cancer and a breast cancer CRF should be returned. All breast cancer pathology must be reviewed by a pathologist approved by the UK National Breast Screening Programme or foreign equivalent. In addition, 20 slides and/or blocks will be required in consenting women for all tumours of breast, ovary or endometrium developing after entry into the trial.

It is recognised that breast cancer mortality is an important secondary endpoint and this will also be analysed. However, the power to detect this within 10 years is marginal and an overview of other similar trials will be needed to obtain clear results on this question. Total and cause-specific mortality will be analysed and the final report form should be returned for any woman who dies of any cause while on therapy.

All women will be followed up for cancer incidence and cause of death using available national tracking systems. During the period of active follow-up (5 years) other serious medical conditions will also be recorded including myocardial infarction, thromboembolic events (superficial and deep), other cardiovascular events, osteoporosis, fractures, other cancers and eye problems. Basic information on prescriptions and hospital visits will also be recorded to facilitate an overall cost-benefit analysis of these interventions.

6.3. Numbers of Volunteers and Power

The total sample size for the DCIS patients will be 4,000. An additional 6,000 women will be recruited into the parallel Prevention trial (3000/arm).

Three factors determine the numbers needed for this study. They are (i) the absolute risk level of the participants, (ii) the size of the smallest reduction thought to be worthwhile and (iii) compliance rates. We also assume a risk of 6 cases of new contralateral breast cancer per 1,000 women per year and similar percentage reductions as above for tamoxifen and anastrozole. The expected number of new cancers in each arm after 5 years of median follow-up is shown in Table 2. These numbers are calculated on the assumption that the local 5 year recurrence rate would be 10% in the absence of systemic treatment, that tamoxifen would reduce it by 40% and anastrozole by 50% (16% relative reduction). Calculations are also made assuming that anastrozole reduces recurrence rate by 60% (33% relative reduction compared to tamoxifen).

Table 2. Expected number of events after a median follow-up of 5 years for IBIS-II (DCIS)

Patients/ Arm	Subgroup	Tamoxifen (40% reduction)	Anastrozole (50% reduction)	Anastrozole (60% reduction)
2000	Local Recurrence	120	100	80
	Contralateral	36	30	24
	Total	156	130	104

Assuming a 50% reduction for anastrozole and 40% for tamoxifen, the non-inferiority of anastrozole (upper 95% CI less than 1.25) can be reliably established at 5 years median followup (Table 3). For all events the power is 93% and for all local recurrences it is 85%. If the reduction associated with anastrozole is 60%, there is adequate power to show the superiority of anastrozole after 5 years for all events (90%), and reasonable power for local recurrence alone (81%).

Similar power (slightly lower) would be obtained if the reduction for tamoxifen was 30% and that for anastrozole 50%. Greater power and earlier analyses may be possible for the DCIS trial by combining data with a similar trial planned in North America.

Table 3.

Power calculations for non-inferiority and superiority of anastrozole over tamoxifen after 5 years median followup

Case I: 40% reduction for tamoxifen

50% reduction for anastrozole

Subgroup	Expected Events	Power non-Inferiority (%)	Power Superiority (%)

Local Recurrence	120 v 100	85	27
Contralateral	36 v 30	49	11
Total	156 v 130	93	34

Case II: 40% reduction for tamoxifen

60% reduction for anastrozole

Subgroup	Expected Events	Power non-Inferiority (%)	Power Superiority (%)
Local Recurrence	120 v 80	>99	81
Contralateral	36 v 24	69	34
Total	156 v 104	>99	90

6.4. Data Monitoring

Monitoring of the data will be undertaken at 6 monthly intervals and summary analyses will be provided to the Independent Data Monitoring Committee (IDMC). No formal interim analyses are planned. This Committee will have the responsibility to recommend to the Steering Committee whether to stop the study early. As a general guideline, a difference between arms should exceed three standard deviations for some mortality endpoint before a decision to stop prematurely is taken, although other factors will also have to be taken into consideration. The Steering Committee will be responsible for the final decisions on such issues. All SAEs should, in addition to the study documentation, be reported to the IBIS Co-ordinating Centre immediately, and subsequently to the IDMC.

6.5. Unblinding the Randomisation

The study is a double blind, double dummy, randomised trial i.e. neither the doctor nor the woman will know who is on active treatment.

The treatment code should only be broken in the following circumstances:

- 1) Where the woman develops breast cancer including new or recurrent DCIS.
- 2) Where it is considered necessary by any clinician involved in her care.

The necessity for verbal code breaking is highly unlikely and open to misunderstanding; therefore the usual procedure will be for a written request to the trial centre with precise details of the situation.

Further information about this code breaking policy can be obtained from the IBIS-II Co-ordinator (+ 44 (0) 20 7014 0246) during working hours or your national coordinating centre for non-UK participants.

Where required by designated national sites, access to the information for code breaks will be available via the IBIS-II website.

7. Consent and Ethics Committee Approval

The study has been approved by the North West Multi-centre Research Ethics Committee (MREC). The study will also require approval by Local Research Ethics Committees (LRECs) of participating centres.

This study involves evaluation of medicines for an unlicensed indication and is being carried out under EudraCT no. 2004-003992-35. Non-negligent indemnity for women joining the study will be provided worldwide by Queen Mary's University London.

All women interested in participating in the study will receive a patient information sheet (PIS) that explains the purpose of the study and warns of the potential short term and long term side effects of tamoxifen and anastrozole. The clinician will clarify and discuss any points arising from the information literature. Participants will then be required by the clinician, research nurse or local coordinator to sign an informed consent form (CF) prior to undergoing any tests. If necessary, the participant may then re-discuss the study with the clinician, who will then counter-sign the CF. Further information and counselling will be made available throughout the study in response to a woman's request or following significant new information on the side effects of tamoxifen or anastrozole. This will be provided by the clinician or the research nurse appointed for this study. All women will be free to stop treatment at any stage, and it will be made clear that leaving the study will not prejudice any future management which may be needed.

Women will be asked to consent

- i) to join the study,
- ii) to have their past and future medical records, mammograms, etc. examined, including those in a cancer registry or death certificate,
- iii) to the storage of personal information for the purposes of the study,
- iv) for a blood sample at entry and on follow-up for risk factor biomarkers and study of genes related to disease risk,
- v) to access to any pathology specimen for anonymous testing for factors related to disease or side effects,

- vi) to receive additional questionnaires from time to time to obtain further relevant information.

All research tests involving DNA or immunohistochemistry will be performed blindly on a case-control basis and results will not be linked to individuals. Thus, it will not be possible to inform women of the results of any tests because of the anonymous nature of all testing.

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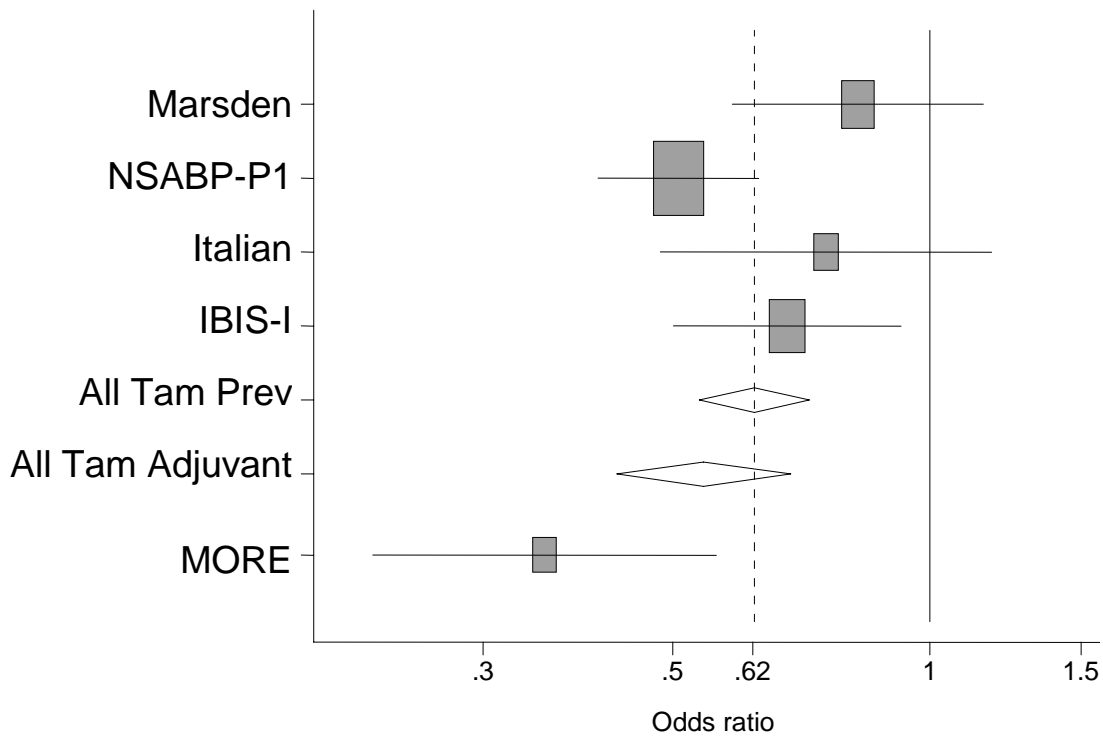
Appendix 1

Breast cancer prevention trials

Trial (entry dates)	Population (size)	Agent (vs Placebo)	Intended Duration of Treatment
Royal Marsden (1986-1996)	Increased Risk Family History (2,471)	Tamoxifen 20mg	5-8y
NSABP-P1 (1992-1998)	1.6% 5y risk (13,388)	Tamoxifen 20mg	5y
Italian (1992-1997)	Normal Risk Hysterectomy (5408)	Tamoxifen 20mg	5y
IBIS-I (1992-2000)	>2-fold risk (7,139)	Tamoxifen 20mg	5y
MORE (1994-1998)	Normal Risk Osteoporotic Postmenopausal (7705)	Raloxifene 60mg Or Raloxifene 120mg	3y

Appendix 1 (cont)

Summary Results of Prevention Trials



Forest plot of estimates of breast cancer incidence reduction for the prevention trials. The summary estimate for all the tamoxifen trials is OR = 0.62 (95% CI (0.54-0.72)), P, 0.001. Test of heterogeneity for all tamoxifen trials gives P=0.09. However the result of the MORE trial are clearly different (Cuzick et al 2003).

Appendix 2

Summary of Drug Handling Guidelines

Astra Zeneca Responsibilities:

The drug handling company IPS(A) will supply to the IBIS London Office. The two formulations used in the trial will be packaged as bulk primary packs, in boxes of 100, and labelled with batch numbers and expiry dates of the product. Each primary pack will contain 224 tablets in an HDPE (High Density Poly ethylene) bottle.

The Active and Placebo tamoxifen will be supplied in medium 160ml HDPE Bottles. The Active and Placebo anastrozole will be supplied in Small 75ml HDPE Bottles. Both bottle types will be capped with tamper evident child resistant lids.

Drug supplies for the study will be stored below 30°C, with the placebo formulation separated from the active formulation.

IBIS Central Coordinating Centre Responsibilities:

These are fully described in the Investigational Product Ordering, Labelling, Supplying, Handling & Storage for IBIS-II Clinical Trial Standard Operating Procedure (SOP)

Appendix 3

Summary of Randomisation and Data Management Guidelines

All data will be treated as confidential and managed in accordance with the provisions of the Data Protection Act.

Each Centre in IBIS-II will run the same software as used at the CR-UK. But whereas at the CR-UK the data is stored in an Oracle database, the centres will usually, though not necessarily, be storing their data in an Access database. As part of the trial program, a centre randomises remotely by simply entering the woman's details and clicking randomise. A connection is made automatically to Mercury, the CR-UK FTP computer, and logged in to its own private space. The program sends the encrypted details then checks every 5 seconds for a reply, up to 40 seconds, until an encrypted file appears for it to download. On download the file is decrypted, the data automatically entered onto the user's form and the database is updated.

At the CR-UK the data file is decrypted, checked against Oracle, entered if a new recruit, and the study number is returned in an encrypted file for the centre to retrieve. Requests for information from the centre are dealt with in the same way. Everything is logged.

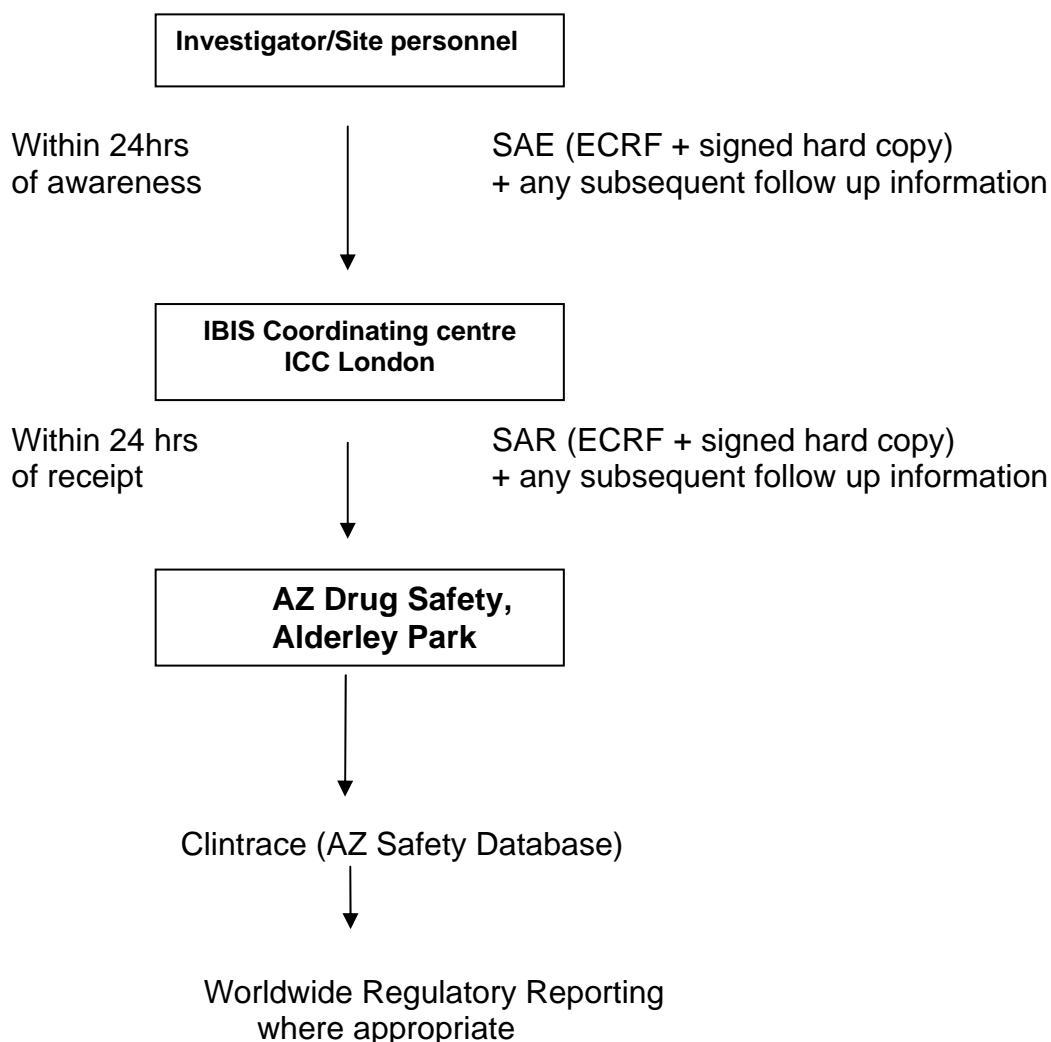
If the centre's computer is down they may request randomisation by email. If all else fails, randomisation can be done by fax and failing that, by telephone.

For further details, please refer to the full IBIS-II Randomisation and Data Management Guidelines.

Appendix 4

Please see Draft for comments 21 March 2004 MRC/DH joint project to codify good practice in publicly funded UK clinical trials with medicines for further guidance

Flow diagram 1 Reporting of a Serious Adverse Event (SAE) by CCO to relevant authorities



Follow up information on an SAE must be reported by the investigator to the CCO in 24 hours and by CCO to AZ in the same time frame as the initial report. i.e. 24 hours since receipt from investigator. 24 hour deadline refers to a timeline within the normal working hour schedule. AZ may request specific follow up information which will be sent to the Investigator via the ICC.

CCO will forward to AZ Drug Safety AP a line listing of all SAEs (related and unrelated) and all non serious AEs every 6 months.

In addition, all SAE (non related, and therefore previously not reported to AstraZeneca on expedited basis) must be reported on a SAE report form along with a completed supplementary form. These pages must be sent 6 monthly along with the line listing.

For further details please refer to the Operational Guidelines

