JRMO Research Protocol for Research Studies

Full Title	Observational Long-term follow up study of participants from the IBIS-II DCIS and Prevention clinical trials
Short Title	IBIS-II-O
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IRAS Number	258590
REC Reference	**19/LO/0984**
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1. Contents

2. Protocol/study document amendment history

Version	Reason	Summary	Section	Pg	Approval	IRAS/REC
1.0 May 2019	n/a -original protocol				30/07/19	IRAS: 258590 REC: 19/LO/0984
2.0 Apr 2021 SA1	Re-activation of protocol post suspension of study Sept 2019	General update of references	6 and 11			
		Method of alerting participants to protocol change added	9	17		
		Study procedure section revised to clarify data analysis	10.11	24		
		Change of study statistician	17	34		
		Addition of IBIS-II TSC member	17	34		
		Added – 'Statistical considerations'	11	24		
		End of study date amended to October 2026.	5	7		
		Addition of protocol/study document change table	2	3		
		Participant opt out procedure clarification	6.3	13		
		Update of section 251 support history	10	18		

Glossary

APR	Annual Progress Report
BCC	Barts Cancer Centre
CCO	Central Coordinators Office
CAG	Confidential Advisory Service
CCG	Clinical Commissioning Groups
CI	Chief Investigator
COD	Cause of Death
CRF	Case Report Form
eCRF	Electronic Case Report Form
CSR	Clinical Study Report
CTIMP	Clinical Trial of Investigational Medicinal Product
DARS	Data Access Request Service
DSA	Data Sharing Agreement
DMP	Data Management Plan
EUDRACT	European Union Drug Regulating Authorities Clinical Trials
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HRA	Health Regulatory Authority
ICF	Informed Consent Form
ICD Code	International Classification of Diseases Code
ICH	International Conference on Harmonisation
ISRCTN	International Standard Randomised Controlled Trials Number
JRMO	Joint Research Management Office
LPLT	Last Patient Last Treatment
NHS REC	National Health Service Research Ethics Committee

NHS R&D	National Health Service Research & Development
NCT	National Clinical Trial number
MREC	Medical Research Ethics Committee
Participant	An individual who takes part in a clinical trial
PTQ	Post Treatment Questionnaire
PI	Principal Investigator
PID	Patient Identifiable Data
PPI	Patient Public Involvement
QMTAG	Queen Mary Trials Advisory Group
QMUL	Queen Mary University London
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee

3. Signature page

Chief Investigator Agreement

The study, as detailed within this Research Protocol (v2.0) will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, and the Declaration of Helsinki and any other applicable regulations. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

Chief Investigator name: **Professor Jack Cuzick**

Signature: 

Date: **11/06/2021**

Statistician's Agreement

The study as detailed within this research protocol will be conducted in accordance with the current UK Policy Framework for Health and Social Care Research, the World Medical Association Declaration of Helsinki (1996), Principles of ICH E6-GCP, ICH E9 - Statistical principles for Clinical Trials and ICH E10 - Choice of Control Groups.

I take responsibility for the statistical work in this protocol is accurate and take responsibility for statistical analysis and oversight in this study.

Statistician's name: **Professor Rhian Gabe**

Signature: 

Date: **11/06/2021**

4. Summary and synopsis

Short title	IBIS-II-O
Methodology	Observational
Objectives / aims	Long-term follow up of participants from the IBIS-II studies (Prevention and DCIS) to understand long term benefits and risks of anastrozole; **Prevention cohort:** To determine if anastrozole is effective in preventing long-term breast cancer in postmenopausal women at increased risk of the disease. **Ductal Carcinoma in Situ (DCIS) cohort:** To determine if anastrozole is at least as effective as tamoxifen in long-term local control and prevention of contralateral disease in women with locally excised ER or PgR positive DCIS.
Number of participants	Approximately 3000 UK participants
Inclusion and exclusion criteria	**Inclusion** · Randomised to treatment in IBIS- II Prevention or DCIS studies · Participant known to be alive · Has given valid consent to participate in compliance with local and national requirements · Participant's local IBIS-II study site is closed to the IBIS-II Prevention and DCIS CTIMP study protocols **Exclusion** · Participant death has been reported to the study during their participation in the IBIS-II Prevention and DCIS CTIMP study · Participant has withdrawn consent to participate in IBIS-II studies and withdrawn consent to digital registry flagging in the IBIS-II Prevention and DCIS CTIMP study · Participant known to have emigrated
Statistical methodology and analysis	The Prevention and DCIS cohort will look at treatment superiority comparing anastrozole with placebo and between anastrozole and tamoxifen. For all analyses, the nominal significance level will be 5% (0.05) for a two-sided test. The log rank test will be used as the primary analysis to provide a basic comparison of treatment groups without adjusting for any potential prognostic factors. An estimate of hazard ratio with 95% confidence limits will also be computed for this analysis.
Study duration	Oct 2021 to Jun 2026

5. Introduction

The International Breast Cancer Intervention Studies (IBIS) have been investigating the use of preventive agents for breast cancer since 1992. IBIS-I initially investigated the use of tamoxifen versus placebo for women with increased risk of developing breast cancer (J. Cuzick et al., 2002). IBIS-II (Prevention) advanced this work by comparing anastrozole versus placebo in a randomised, double-blind control trial in women at increased risk. A companion protocol was also developed (IBIS-II DCIS) to compare anastrozole to tamoxifen for women with locally excised oestrogen receptor-positive (ER) or progesterone receptor (PgR) positive Ductal Carcinoma in Situ (DCIS).

Over 14,000 women have now been enrolled on to an IBIS study and they continue to generate novel and high-impact outputs of international interest (Brentnall et al., 2016; J. Cuzick, 2003; J. Cuzick et al., 2002; J. Cuzick, Sestak, Cawthorn, Hamed, Holli, Howell, & Forbes, 2015; J. Cuzick, Sestak, Cawthorn, Hamed, Holli, Howell, Forbes, et al., 2015; J. Cuzick et al., 2014; Forbes et al., 2016; I. Sestak et al., 2012; Singh et al., 2007; Singh, Cuzick, Mesher, Richmond, & Howell, 2012; S. G. Smith, Sestak, Howell, Forbes, & Cuzick, 2017; Samuel G. Smith et al., 2021) (Jack Cuzick et al., 2020; Ivana Sestak et al., 2019) (Ivana Sestak et al., 2021; Sestak I, 2020).The findings have directly contributed to shaping national guidelines for the management of women at increased risk of developing breast cancer (NICE recommendation CG164). The IBIS-II studies have been running at sites globally since 2003. Whilst the active treatment period of both the IBIS-II studies concluded in 2017, the IBIS-II team continues to collect data from participants to assess the long-term efficacy and serious side effects of tamoxifen and anastrozole via annual questionnaires (in Italy, France, Australia, and New Zealand) and digital registry flagging (in UK).

Long-term follow up is important to fully determine the benefits and risks of preventive agents, as divergence between treatment groups may not become apparent until decades after the intervention has stopped (J. Cuzick, Sestak, Cawthorn, Hamed, Holli, Howell, & Forbes, 2015). However, collecting follow-up data over extended periods is complex, expensive, and challenging to both trialists and participating sites (Kilburn, Banerji, Bliss, & Group, 2014).

Given the greatly reduced risk profile of the IBIS-II studies at this stage, it is important to optimise and rationalise current data collection methods. This protocol specifically aims to collect data via remote 'flagging' using the UK national digital data registries for IBIS-II UK participants, enabling the IBIS-II team to close the CTIMP study at local research sites and follow up the cohort centrally.

Closed international IBIS-II sites who wish to continue providing follow-up data can utilise this protocol for long-term data collection for their participants. In addition, a data sharing agreement will be set up between each international site and QMUL, should they wish to provide longitudinal data (See Appendix 2). However, this protocol is

designed to meet the study objectives for the UK cohort only and international data contribution will be considered supplemental.
The aim of this protocol is to provide a sustainable platform to collect long-term outcome data from IBIS-II participants over extended periods whilst continuing to meet the scientific objectives set out in the IBIS-II Prevention and DCIS protocols beyond the current end of study definition in 2022.

5.1. Background

Long-term follow-up is an important unmet need required to improve our understanding of treatments for breast cancer. Earlier detection of cancer and more effective treatments have led to many more patients surviving for more than 10 years. Therefore evaluating late (re)-occurrences and side-effects is an increasingly important issue (J. Cuzick, Sestak, Cawthorn, Hamed, Holli, Howell, & Forbes, 2015). This is particularly relevant for ER-positive breast cancer, where the occurrence of late recurrences is well documented. The Oxford Overview (Ingle, 2007) has provided useful data on follow-up for 15-20 years after tamoxifen therapy, showing that a large proportion of women with good prognosis tumours develop late recurrences. However, such data are lacking for aromatase inhibitors (AIs). This protocol provides an opportunity to address this issue in the preventive setting and for those with early stage, non-invasive breast cancer.

Several key studies in the prevention and adjuvant treatment setting for breast cancer underpin this protocol. The IBIS-I trial investigated the efficacy of tamoxifen in preventing breast cancer development in women at increased risk of developing the disease (J. Cuzick et al., 2002). Since tamoxifen has shown to have a long-term beneficial effect on breast cancer development (J. Cuzick, Sestak, Cawthorn, Hamed, Holli, Howell, Forbes, et al., 2015) continued long-term efficacy of tamoxifen is currently ongoing to determine whether the beneficial effects continue past 20 years since randomisation to the study. The ATAC trial (Arimidex, Tamoxifen Alone or in Combination) compared tamoxifen, anastrozole and the combination of the two drugs for five years in breast cancer patients with hormone receptor positive disease (Howell et al., 2005). The IBIS-II Prevention and IBIS-II DCIS have both published results reporting efficacy of anastrozole in comparison with tamoxifen (DCIS) or placebo (Prevention). (Jack Cuzick et al., 2020; J. Cuzick et al., 2014; Forbes et al., 2015; Ivana Sestak et al., 2021; Sestak I, 2020)

Both the ATAC trial (now running as an epidemiologic follow up study know as LATTE: NCT01745289, ISRCTN86305500) and IBIS-I studies (now running as IBIS-I Epidemiological - NCT00002644, ISRCTN91879928, EUDRACT 2005-003091-38) continue to monitor their cohorts to further understand the long-term benefits and effects of these drugs using data collected from various national digital registries.

IBIS-II Studies

IBIS-II studies continue the work started in IBIS-I by examining the role of anastrozole in the prevention of breast cancer with the aim to reduce breast cancer incidence by even more than tamoxifen with potentially fewer serious side effects.

Prevention

The Prevention study has been running since 2003. A randomised, placebo-controlled trial of 3864 postmenopausal women with increased risk of breast cancer were randomised to either anastrozole or a placebo for 5 years. In 2013, the initial results were published after a median follow up of 5 years (IQR 3.0–7.1); 40 women in the anastrozole group (2%) and 85 in the placebo group (4%) developed breast cancer (hazard ratio (HR) 0.47 (95% CI 0.32–0.68), p<0.0001). These results showed that women taking anastrozole were 53% less likely to develop breast cancer than those on placebo. Sustained follow up is required to see if this difference persists and if there is further diverge between the treatment arms (J. Cuzick et al., 2014).

Anastrozole has been shown to substantially reduce incidence of breast cancer in high-risk postmenopausal women. This finding, along with the fact that most of the side effects associated with oestrogen deprivation were not attributable to treatment, provides support for the use of anastrozole in postmenopausal women at high risk of breast cancer which has now been recommended by NICE.

Women randomised to anastrozole experienced more joint, bone, muscle aches, and more hot flushes than those on placebo. There was a small increase in fractures with 164 (9%) reported for women receiving anastrozole compared with 149 (8%) in the placebo group. In addition, it was found that women receiving anastrozole were less likely to develop other cancers with 40 cases being found in women taking anastrozole compared with 70 reported in the placebo group. The reasons for this were unclear and need further research.

After a median follow-up of 10.9 years (Jack Cuzick et al., 2020) women assigned to anastrozole were 50 percent less likely to have developed breast cancer compared with women assigned to the placebo. No new adverse side effects or an increase in known side effects were added to those reported in 2013, which were mostly small increases in muscle aches and pains, and hot flashes.

The 50 percent reduction in likelihood of breast cancer incidence after 10.9 years of follow-up is slightly less than the 53 percent reduction reported after the first seven years of follow-up, but it is still a significant effect and larger than that seen for tamoxifen (Cuzick, Sestak, Cawthorn, Hamed, Holli, Howell, Forbes, et al., 2015).

At the time of analysis, 129 deaths had been reported, with no significant difference in all-cause mortality between the anastrozole and placebo groups. For breast Cancer mortality, five deaths were reported, two among those assigned anastrozole and three

among those assigned placebo, which are too few to determine if anastrozole reduces breast cancer mortality. To answer this question longer follow up is required.

DCIS

Published results from the DCIS trial at a median follow up of 7.2 years revealed no statistically significant difference between anastrozole and tamoxifen in overall recurrence (67 vs. 77; HR=0.89 (95% CI 0.64–1.23): p=0.49) (Forbes et al., 2015). However, a similar trial conducted in the United States with a median follow up of 9 years reported 122 recurrences in the tamoxifen group and 90 in the anastrozole group (HR=0.73 (95% CI, 0.56–0.96); p=0.02), with a significant time-by-treatment interaction (p=0.041). The beneficial effect of anastrozole over tamoxifen only became evident later in this study with increasing median follow-up time (Margolese et al., 2015).

After a median follow-up of 11.6 years (Sestak I, 2020), the cumulative incidence of breast cancer recurrence was 8.5% in the anastrozole group and 9.7% in the tamoxifen group, translating into a non-significant risk reduction of 11% with the aromatase inhibitor.
These findings were consistent with those from the first 5 years of follow-up when patients were on active treatment. Specifically, the rates of breast cancer recurrence were 2.6% and 3.0% among anastrozole- and tamoxifen-treated patients, respectively; giving a non-significant 16% reduced risk for recurrence with anastrozole.

When stratified by type of breast cancer recurrence, anastrozole treatment was associated with a marginally significant 44% reduction in the risk for HR-positive disease relative to tamoxifen during the active treatment period, but this was not apparent in the post-treatment period.

Reporting on toxicities, fractures were a significant 34% more likely among patients treated with anastrozole versus tamoxifen, and the risk for cerebrovascular accident or stroke and transient ischemic attack were also a significant threefold higher with anastrozole. By contrast, tamoxifen was associated with a significant 83% and 87% increased risk for endometrial and ovarian cancer, respectively, compared with anastrozole.

Anastrozole offers an improved treatment option for postmenopausal women with hormone-receptor positive DCIS, which may be more appropriate for some women with contraindications for tamoxifen.

IBIS-II Long term follow-up

After achieving the Last Patient Last Treatment (LPLT), the IBIS-II team took this milestone as an opportunity to review the current protocol objectives and to determine that analysis of the long-term efficacy of anastrozole requires ongoing data collection. Statistical review of the sample size calculations based on current participant retention

and event reporting highlighted that a reduced sample size would be sufficient to meet the primary objectives and therefore a number of international sites were closed. As of 2019, the UK, Australia, New Zealand, France and Italy remain open providing the majority of current participants (77% of IBIS-II Prevention cohort and 46% of IBIS-II DCIS cohort). (Table 1).

Table 1. Origin of IBIS-II Cohort 2019

	Prevention	DCIS
Original cohort (Total)	3864	2980
UK*	2157	883
Italy**	175	255
France**	0	105
Australia and New Zealand (ANZ)**	669	129
Current Follow up cohort (Total)	3001	1372

* Active follow up and flagging ** Participants alive and in active follow up

IBIS-II Digital Registry Follow up

Since 2012, the IBIS-II studies have used 'flagging' to track UK participants remotely via NHS Digital, NHS Services Scotland (NSS), NHS Welsh Informatics Service (NWIS), and Northern Ireland Cancer Registry (NICR) registries including the Cancer Registry, Death registry from the Office of National Statistics (ONS), Hospital Episode Statistics (HES) for Admitted patient Care (APC), Accident and Emergency (AE) and Outpatients. This information was used to supplement annual data collection at the local IBIS-II sites and participants have had the option to be followed by registry flagging only since this time. All participants have consented to flagging, but because of changes in requirements in the consent wording, it was necessary for the IBIS-II team to make an application to the Confidentiality Advisory Group (CAG) for section 251 support relative to the usage of the data for the entire cohort (Prevention 20/CAG/0135, DCIS 20/CAG/0134) application was successful.

5.2. Rationale

Research indicates that anastrozole has a long-term protective effect against new and recurrent ER-positive breast cancers superior to the effects of tamoxifen (J. Cuzick, Sestak, Cawthorn, Hamed, Holli, Howell, Forbes, et al., 2015) Extended follow up is needed to see if this is maintained as was the case for tamoxifen. This protocol aims to collect long-term follow-up data beyond the current end of trial definition in the IBIS-II Prevention (EudraCT 2004-003991-12/MREC 02/8/70) and DCIS (EudraCT 2004-003992-35/MREC 02/8/71) CTIMP protocols to determine the long-term efficacy of anastrozole and tamoxifen.

The IBIS-II cohort is already established, and by extending the follow-up period with this protocol, the IBIS-II team can accurately assess the long-term objectives for the DCIS and Prevention cohorts. In addition, this study will further assess the carry-over

benefits of anastrozole like that seen with tamoxifen in IBIS-I (J. Cuzick, Sestak, Cawthorn, Hamed, Holli, Howell, Forbes, et al., 2015).

Increasing numbers of participants are lost to clinic follow up in the main IBIS-II studies and finding completion of annual post treatment questionnaires (PTQs) an increasing burden. Therefore, it is important to utilise other methods of data collection to meet the study objectives. There are around 3000 participants from all UK sites, but of these, only 1.2% (38) have withdrawn consent for remote flagging. Therefore, the vast majority of the cohort can be followed up with this more efficient method.

An initial comparison of breast cancer events and mortality data, received from the National Health Service (NHS) Digital, covering the time span from January 2000 to March 2016, showed that the registry data largely confirmed patient-reported breast cancer events. We were also able to identify breast cancers and deaths in participants who had been lost to follow-up or had withdrawn from direct contact. This furthermore indicated the potential to identify significantly more secondary endpoints (other cancers and clinical events) (M.L. Sleeth, 2018).

5.3. Risks / benefits

UK Participants

It is important to continue to study the effects of anastrozole in the prevention and DCIS setting to improve understanding of long-term efficacy. Overall, this study protocol has no direct patient contact or intervention, meaning a minimal risk to participants. By collecting outcome data via the digital registries in the UK, this protocol can continue to meet the original objectives of the IBIS-II studies whilst eliminating the burden on local sites and participants.

All IBIS-II participants completed the intervention phase of the study in 2017. The safety profile of anastrozole and tamoxifen is well established and the National Institute of Healthcare Excellence (NICE) recommends offering both agents for use in breast cancer prevention (National Institute of Clinical Excellence, 2019). With continued collection of treatment related events, including other cancers, bone fractures and cardiovascular events, we can continue to monitor the known safety profile in the long-term setting without the need for formal pharmacovigilance.

For UK participants, long-term follow-up data is collected via the national digital registries. However, if insufficient data is reported from the registries e.g., missing ER, PgR or HER2 status, the participant's GP may be contacted. Copies of all UK IBIS-II participant consent forms are held at the central coordinators office (CCO) and will be provided to GPs as evidence of their taking part in the trial.

UK Participants have previously been informed that they are being followed up remotely and this may contribute to a sense of altruism, but there are no direct benefits

to individual participants at this time. Part of the recent UK site closures in 2020, participants were reminded of the flagging process in both a letter from the site and the latest study newsletter.

There is a clear opt-out procedure if participants wish to withdraw from further follow-up detailed on the patient website (https://www.ibis-trials.org/healthsurveillance) including a postal address that participants can write to should they wish to withdraw or contact the study team. This information is also included in all participant updates and newsletter communications. The website is regularly monitored by the IBIS-II team and all requests to opt out of long-term flagging will be executed and confirmed with the participant within 10 working days. The IBIS-II team will write to participants intermittently to inform them of important outcomes and publications related to their participation in the study. All UK participants have given permission to have their details held centrally and to be contacted by the IBIS-II team.

International participants

For international participants, data collection will come from local medical records, registries or questionnaires. International sites need to obtain local sponsorship and a clear data sharing agreement should be in place to define how the site will collect and validate the follow up data and ensure all patients have provided informed consent. A copy of any approved documents must be filed in the trial master file (TMF).

Data integrity

The aim is to follow up this cohort until comparable median follow-up time reported in IBIS-I (median follow-up 16 years at last publication) has been achieved to evaluate the long term efficacy/safety of anastrozole (J. Cuzick, Sestak, Cawthorn, Hamed, Holli, Howell, Forbes, et al., 2015) and the long term value in the DCIS setting (Forbes et al., 2015).

In the UK, this study involves the exchange of patient identifiable data (PID) between the study team and the digital registries in order to meet the study objectives (See Section 6). It is therefore necessary to ensure robust technical and organisational measures are in place to maintain and respect participant's rights. A comprehensive data management plan (DMP) will detail the specific procedures required to collect, import, and integrate the data and will be maintained throughout the course of the study.

Sleeth et.al (2018) reported that flagging added minimal benefit to primary end-point data compared to active methods and very few breast cancer and DCIS cases were identified through passive methods when compared with data collected from IBIS-II sites. However, significant value was identified with regards to secondary trial end-points (including other primary cancers of interest and deaths) which had not been

previously identified through active follow-up were found (20% of secondary events identified).

In order to maximise accurate data collection, the IBIS-II team will work with data providers to minimise future linkage failures. Data collection through registries offers clear financial and logistical benefits over active follow-up.

All PID is stored, encrypted, on a local Oracle database separate from the clinical data and only accessible by authorised personnel. Original 'raw' data sets returned by the national registries containing PID will be stored on a separate server, meeting security requirements as outlined by the provider's data sharing agreement.

There is a risk that data collected locally may not be complete or accurately reported, and therefore we may need to be much more reliant on digital registry data. Thus, it is important to be confident in the quality of the data. Reporting of fully staged tumour data has increased dramatically in the last 12 years (completeness of stage at diagnosis is over 80% for breast cancers (PHE, 2014)). Data reported by Lucy Elliss-Brookes from PHE in 2018 showed that staging of reported malignant cancers has increased 6-fold since 2004 (16% to 87%). It is therefore reasonable to assume that registry data provided in the UK is suitable to meet our study objectives (L. Elliss-Brookes, 2018).

6. Study objectives

6.1. IBIS-II Prevention objectives

Table 2. IBIS-II Prevention objectives

Objectives		Endpoint	Measure
Primary	To determine if anastrozole is effective in preventing breast cancer in postmenopausal women at increased risk of the disease	Breast cancer	Data from digital registry or local pathology report with histologically confirmed breast cancer, both invasive and non-invasive (i.e. including DCIS) when registry data is not sufficient
Secondary	To examine the effect of anastrozole on breast cancer mortality	Death from breast cancer	COD and date confirmed via data registry
Exploratory	To examine the role of anastrozole in preventing oestrogen receptor positive breast cancer.	ER-positive breast cancer	Data from digital registry or local pathology report with histologically confirmed breast cancer, both invasive and non-invasive (i.e. including DCIS) when registry data is not sufficient.
	To examine the effect of anastrozole on other cancers, cardiovascular disease, fracture rates, and non-breast cancer deaths.	Ischaemic cardiac and cerebrovascular events, hip (and other) fractures	
		Serious cardiac or cerebrovascular events (such as myocardial infarct or stroke; not angina or transient ischaemic attack), all hip and other fractures	

6.2. IBIS-II DCIS objectives

Table 3. IBIS-II DCIS objectives

	Objectives	Endpoint	Measure
Primary	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.	DCIS Recurrence or primary breast cancer	Data from digital registry or local pathology report with histologically confirmed breast cancer, both invasive and non-invasive (i.e. including DCIS) when registry data is not sufficient.
Secondary	To examine the effect of tamoxifen vs anastrozole on breast cancer mortality	Death from breast cancer	COD and date confirmed via data registry
Exploratory	To compare the effectiveness of tamoxifen and anastrozole according to the receptor status of the primary or recurrent cancer.	Oestrogen receptor positive breast cancer	Data from digital registry or local pathology with histologically confirmed breast cancer, both invasive and non-invasive (i.e., including DCIS) when registry data is not sufficient.
	To examine the rate of breast cancer recurrence and new contralateral tumours after cessation of tamoxifen or anastrozole.	New breast cancer	
	To examine the effect of tamoxifen and anastrozole on other cancers, cardiovascular disease, fracture rates, and non-breast cancer deaths.	Ischaemic cardiac and cerebrovascular events, hip (and other) fractures	
		Serious cardiac or cerebrovascular events (such as myocardial infarct or stroke; not angina or transient ischaemic attack), all hip and other fractures	

7. Study population

The study population are participants recruited in to the IBIS-II trials who have not withdrawn consent for long-term follow-up or data flagging. See Appendix 1 for IBIS-II DCIS/Prevention eligibility criteria.

7.1. Inclusion criteria

1. Randomised to treatment in IBIS- II Prevention or DCIS studies
2. Participant was known to be alive at the point the study closed
3. Has given valid consent to participate in compliance with local and national requirements
4. Participant's local IBIS-II study site is closed to the IBIS-II Prevention and DCIS CTIMP study protocols

7.2. Exclusion criteria

1. Participant death has been reported to the study during their participation in the IBIS-II Prevention and DCIS CTIMP study
2. Participant has withdrawn consent to participate in IBIS-II Prevention and DCIS CTIMP studies
3. Participant has withdrawn consent to digital registry flagging in the IBIS-II Prevention and DCIS CTIMP study
4. Participant known to have emigrated

8. Study design

IBIS-II-O is an observational study designed to capture new breast cancers, recurrences, deaths and specified clinical events (**Error! Reference source not found.** and **Error! Reference source not found.**) in women who previously participated in the IBIS-II DCIS and Prevention trials.

UK Participants were informed of ongoing follow up via digital registries by letter, sent to them when their local IBIS-II site closed to the IBIS-II CTIMP protocol. Clear withdrawal instructions were provided in the letter and study website as detailed in section 6.3 As digital flagging has moved to from the main IBIS-II protocols (DCIS and Prevention) to this protocol, the end of the study has extended to 2026 and Ethics references changed. This will be outlined in the next newsletter in accordance with section 251 CAG support (new ref pending).

All data collected via UK Digital registries from the devolved nations and/or PHE datasets (Figure 1). PID collected during the main Prevention and DCIS studies including name, address, postcode, and NHS number sent to the relevant digital

registry to obtain linkage with their records. Once accurate linkage confirmed, this data integrated into the main IBIS-II DCIS and Prevention datasets.

For international participants, data reported via the original site PI, collected from local registries, questionnaires or medical records should be specified in a data sharing agreement between the CCO and the participating site.

The data from the digital registries is merged with the existing IBIS-II DCIS and Prevention cohort data tables for analysis.

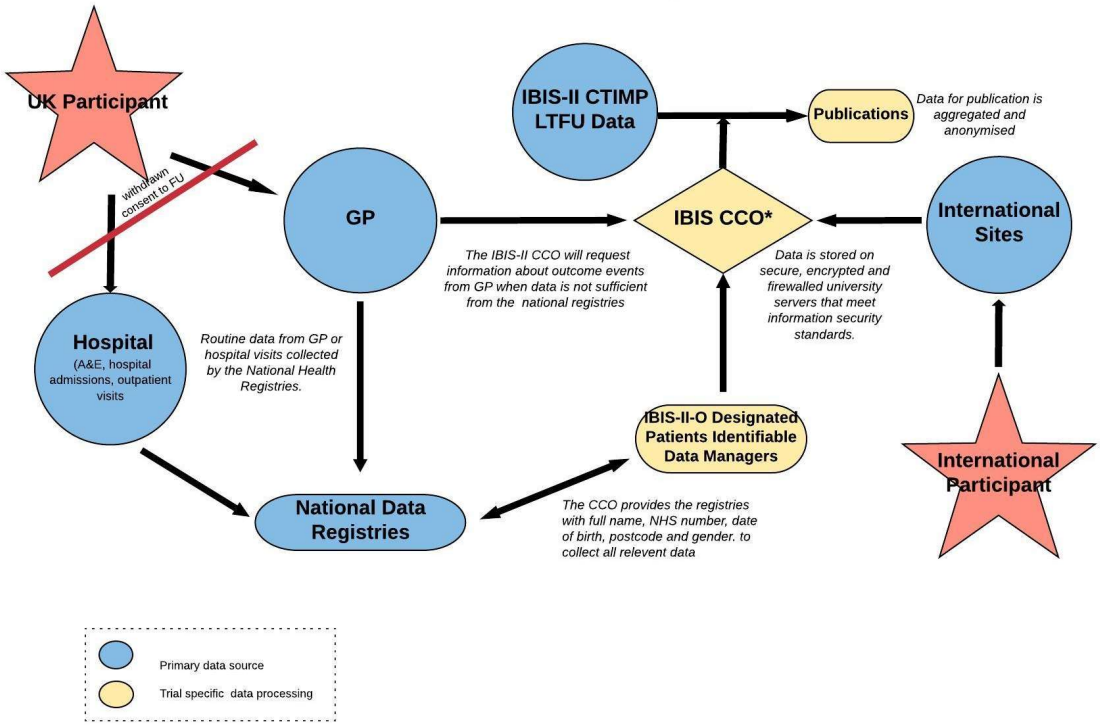

Figure 1: IBIS-II-O Data flow, collection and processing

9. Study procedures

9.1. Consent

UK

Consent has been obtained for long-term follow up as part of the IBIS-II Prevention and DCIS trials. Any IBIS-II participant that gave consent on version 11 of the informed consent form (ICF) for both studies will have consented to ongoing follow up post 10 years. Participants who consented on earlier versions of the consent form were contacted by their local site to seek their consent for follow-up beyond 10 years. Consent was documented via completion of an eCRF at the trial site, taken verbally over the phone, or by paper CRF if the site posted the questionnaires for completion.

In September 2012, CAG approved the study for Section 251 support, which agreed that the study procedures and objectives for which consent was previously obtained were sufficiently similar to allow the study team to track participants via digital registries without seeking additional consent (Prevention 20/CAG/0135, DCIS 20/CAG/0134)

This protocol has the same objectives as the main CTIMP protocols and the risks and burdens of obtaining re-consent in this cohort have been considered with the support and consideration of a Public Participation Involvement (PPI) consultation. In consideration of this, this protocol has additional Section 251 CAG support that specifies that further consent is not required from this cohort 19CAG1926.

Europe/Rest of World

There should be evidence of valid consent before any data can be passed to the CCO. It is the responsibility of the PI to ensure that the consent procedures are compliant with local and national regulations. The site and the IBIS-II team will have a DSA in place which will specify the consent arrangements made by the site.

9.2. Screening and recruitment

There is no screening or recruitment activities as the cohort is already established. Participants will be identified via existing IBIS-II databases. The specific identification method will be detailed in the IBIS-II-O data processing manual and will ensure that only patients meeting the eligibility criteria specified in sections 6.1 and 6.2.

9.3. Data release

Data collection will be kept at a minimum, and only items essential to analyse the specific endpoints listed will be collected. All requests for data release using the IBIS-II-O dataset should be reviewed by the IBIS-II Trial Steering Committee.

9.4. Unblinding

The original IBIS-II Prevention and DCIS CTIMP study protocols are double-blind, placebo-controlled, randomised trials, i.e., neither the doctor nor the woman know their treatment allocation.

Under the original CTIMP study protocols, unblinding is offered when a woman develops breast cancer, if a clinician considers there to be valid medical or safety reasons or when a participant requests unblinding. Participants are not routinely informed to their allocation.

It is important that the IBIS-II-O team remain blinded to the original treatment allocation from the CTIMP protocols to avoid bias in future outcome analyses. Under the IBIS-II-O protocol, the IBIS-II team will continue to offer ad-hoc participant and clinician requested code-break requests. This will be communicated in the newsletter and instructions given on the patient facing website.

9.5. Participant timelines

There is no prescribed visit structure. It is recommended that non-UK sites gather information about their patients' at least at annual intervals. Participant data can be reported at an agreed time once per year or reported as and when the information is obtained. See Table 4.

Table 4. Summary of IBIS-II-O study activities

Study Activity	*Cohort*	*Data Source*	*Frequency*	*Validation*
Collection of follow up data from eligible IBIS-II participants	UK	Digital Registries	Annual	Cancer registry data from PHE (England and Wales only), NICR and NSS. Confirmation of new breast cancers with GP if registry data not sufficient
	Non-UK	Medical records, registries or questionnaires as negotiated in DSA	Annual (recommended)	Confirmation of new breast cancers with PI

9.6. Data collection and storage

Data will be collected annually via the U-based digital registries and as negotiated with the international sites specified in DSAs. No data will be exported outside the EU or UK. Long-term follow-up data received from any participant will be processed and held on a secure Barts Cancer Centre IT network. A collection of the data registry variables will be used to meet the study objectives. See Tables 5, 6 and 8.

Table 5. Events of Interest/ICD code

Event	**ICD-code**
Breast cancer	
Breast cancer (invasive)	C50.0-9
Breast cancer (DCIS)	D05.0/1/7/9
Other malignant cancer	C00-43, C45-49 and C51-97 (all sub-codes) This includes all other cancers except skin
Other events	
Pulmonary embolism	I26.0, I26.9
Deep vein thrombosis	I80.2
Cerebrovascular events	I63 (all sub-codes), I64
Cardiac arrest	I46 (all sub-codes)
Acute myocardial infarction	I21 (all sub-codes), I22 (all sub-codes) I22 is for subsequent myocardial infarctions
Heart failure	I50 (all sub-codes)
Transient cerebral ischaemic attack	G45.8, G45.9
Hypertension	I20, I15 (all sub-codes), I27 (all sub-codes)
Fractures	M80 (all sub-codes), T02.9, T08, T10, T12, S02 (all sub-codes), S12 (all sub-codes), S22 (all sub-codes), S32 (all sub-codes), S42 (all sub-codes), S52 (all sub-codes), S62 (all sub-codes), S72 (all sub-codes), S82 (all sub-codes), S92 (all sub-codes)

Table 6. Examples of cancer data variables

Data item	Relation to study objective
NHS number	Required for record-level data to be linked to specific individuals in our cohort
Date of Birth	Required for record-level data to be linked to specific individuals in our cohort. Survival analysis. To determine the effectiveness of the intervention.
Date of death of the patient	To determine if intervention was successful in preventing cancer incidence
Cause of death	
Diagnosis date	
Diagnosis death certificate only	Primary endpoint confirms participants cause of death
Site of neoplasm	Study endpoint to identify location of cancers
Site of the cancer	
Histology code	
Grade of tumour	Study endpoint to confirm full details of all cancers
Size of the largest dimension of the tumour, in mm	
Number of nodes excised	
Number of nodes involved	
Laterality	
Oestrogen receptor status of the tumour	
Oestrogen receptor score of the tumour.	
Progesterone receptor status of the tumour	
Progesterone receptor score of the tumour	
HER2 status of the tumour	
Excision margin	
Screen detected cancer	
Code for the Trust at diagnosis	Trace origin of diagnosis potentially query Hospital for further details
Name of the trust at diagnosis	

UK

The application process to request data from the national registries is structured to promote compliance with the Data Protection Principles and Information Governance safeguards. Datasets received from the national registries are a compilation of information collected by the following national data service entities:

- Hospital Episodes Statistics (HES), provides the following datasets for:
  - Admitted Patient Care
  - Accident & Emergency Care
- National Cancer Registry
- Civil Registration Mortality data
- Public Health England (PHE)

Table 7. Current digital dataset provision Feb 2019

Organisation	Devolved UK Nation	HES	Mortality	Cancer Registry	Tumour markers
NHS Digital	England/Wales	x	x	x	
NWIS (NHS Wales Information Service)	Wales	x			
NICR (Northern Ireland Cancer Registry)	Northern Ireland	x		x	x
NSS (NHS National Services Scotland)	Scotland	x		x	x
PHE (Public Health England)	England			x	x

The organisation providing data could change throughout the course of the study and a copy of this table reflecting current practice will be maintained in the IBIS-II-O DMP.

Table 8. Digital registry variables

Data source	Variables	Information provided
HES data set variables	GP Code Date of diagnoses Date of diagnoses Description	GP contact details Cardiovascular and cerebrovascular events, new and recurrent breast cancers, other cancers, bone fractures
Cancer registry data set variables	Date of diagnoses Diagnoses Code Description	New and recurrent breast and other cancers including melanomas
Civil Registration Mortality data set variables	IBIS-II Status Date of Death Cause of death	Death and cause of death

Public Health England data set variables	Cancer registry - patient table Cancer registry - tumour table	Tumour markers. TNM staging and grading, ER, PR and HER status of breast cancers

Receiving Data from Digital registries

The original raw data sets are received from the data registry provider through Data Access Request Service (DARS) online for NHS Digital and other digital registry datasets. Once received, the files are saved in a restricted access folder on the Barts Cancer Centre network and imported into Oracle according to the IBIS-II-O DMP.

Unmatched patient details

If an IBIS-II participant's details are incorrect, out of date, or not on file, it may not be possible to ensure a correct match with the relevant digital registry records. If matching fails, effort will be made to identify why and unmatched events should be resolved where possible. If possible, the site team should contact the participant's previous local site if feasible or their GP if details are known.

Extracting data

Raw data extracts from the digital registries either will contain PID or have been linked to the trial study number (SNO) before it is sent. Where PID is sent to the IBIS-II-O research team, a suitably qualified person will pseudonymise the datasets by linking the data to the existing IBIS-II dataset and remove all PID if not previously linked and removed by the data organisation.

The ICD-10 code list of events (Table 5) will be used to match events with further details on deaths, new or recurrent breast cancers from variables listed in Table 6.

Following up with GPs

Follow up with participants' GPs for more information about new or recurrent breast cancers reported via the digital registries will occur if the information provided is not sufficient or where tumour marker data is not available (Wales, Northern Ireland and Scotland).

Additional information obtained from GPs responses should be logged and linked to the SNO only and entered in the IBIS-II-O database. The source of the data should be specified on the Oracle tables.

9.7. International participants

New breast cancers, breast cancer recurrences, clinical events, and deaths will be provided by the PI at least once a year. Event, tumour and staging data will be requested from the participating sites as outlined in Tables 4 and 5. Depending on the

terms of the DSA, the site may provide aggregated data or complete individual CRFs with all necessary information.

9.8. Participant withdrawal

Participants are free to withdraw at any time from the IBIS-II-O protocol. Participants can withdraw from flagging or newsletter updates or both. Participants can also request communication from email only. However, data will not be removed from any analysis that has already been completed and participants have previously been informed of this.

Participants can request to withdraw from further data collection by contacting the IBIS-II team either by phone or completing the online form via the IBIS-II website (https://www.ibis-trials.org/healthsurveillance). The IBIS-II email account is monitored on a regular basis by the IBIS-II team and actioned accordingly. The participant status change will be recorded on the main oracle table according to the IBIS-II-O DMP. Participants will be notified by email or letter within 10 working days that their request to withdraw has been processed and they are no longer being followed up.

9.9. Patients lost to follow up

If no data are received from NHS Digital because either 'no trace' or type 2 objections are upheld, the participant will not be immediately considered lost to follow up for this study. Instead, if data is not collected for a participant in any given year, they will remain on the list of participants for which data is requested until either primary outcome data have been collected or the IBIS-II team considers that sufficient information has been collected to report the final results of the study. If no data further has been reported, they will be reported as lost to follow up in the final analysis.

UK

HES covers all NHS Clinical commissioning groups (CCGs) in England and Wales including private patients treated in NHS hospitals, patients' resident outside of England under care provided by treatment centres, including the independent sector, funded by the NHS. For participants who commenced the CTIMP study in England and moved to either Northern Ireland or Scotland, cross-border transfers will be recorded so they can be followed up via the appropriate national registry (NSS or NICR). Similarly, if participant moved from the devolved nation to England this will also be detected.

International

All attempts should be made by participating non-UK sites to collect follow up data until the agreed end of study definition specified in 8.10 unless a lost to follow up threshold is specified within the DSA.

9.10. End of study definition

This cohort will be followed up until a median of 16 years is reached, which is estimated to be in 2026 in order to provide a comparable follow up period with the IBIS-I study (J. Cuzick, Sestak, Cawthorn, Hamed, Holli, Howell, Forbes, et al., 2015).

9.11. Planned analysis

As well as per-protocol analysis, data collected from the CTIMP protocols will be analysed together with the data from this protocol to provide the final outcome analysis.

Data from this will be combined with the final dataset from IBIS-II DCIS and Prevention for the final outcome analysis for publication.

10. Statistical considerations

The original sample size for the IBIS-II CTIMP trial is given below (11.1) for completeness. The IBIS-II trial recruited the participants and the main results relevant to these sample size calculations have been published (Cuzick et al. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. Cuzick et al., 2014). Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial (Jack Cuzick et al., 2020; Sestak I, 2020). Henceforth, the observational study described in this protocol will continue to collect outcome data described in section 9.6 above, to answer outstanding questions regarding long-term effects of anastrozole in the prevention cohort, and anastrozole compared to tamoxifen in the DCIS cohort with respect to breast cancer incidence, mortality and adverse events. Since this protocol is concerned with observational follow up of a pre-defined cohort, no formal sample size calculation will be performed. The aim is to gather as complete data as possible on these outcomes.

10.1. Sample size

Table 9 shows estimated HRs and number of events for each study separately. In the IBIS-II prevention cohort of 2157 participants, we have 80% power to detect 180 breast cancer events with an HR of 0.65 for anastrozole versus placebo (35% reduction) (alpha=0.05) if the probability of surviving at the end of the study is 90% in the placebo group. We can achieve 90% power (alpha=0.05) and a HR of 0.60 (40% reduction) with minimal of 175 breast cancer events.

For DCIS (N=883), a HR of 0.66 for anastrozole versus tamoxifen can be detected with a power of 80% (alpha=0.05) if the probability of surviving at the end of the study is 75% in the tamoxifen group. This is based on a minimum of 187 detected events.

Table 9. Power calculation

	Prevention	DCIS
Number	2157	883
Events	180	187
Hazard ratio	0.65	0.66
Power	80%	80%
Alpha	0.05	0.05

10.2. Method of analysis

Prevention

Primary/secondary objectives
For all analyses the nominal significance level will be 5% (0.05) for a two-sided test. The log rank test will be used as the primary analysis to provide a basic comparison of treatment groups without adjusting for any potential prognostic factors. The log rank test is equivalent to the Cox proportional hazards model without baseline covariates. To allow an estimate of hazard ratio, associated confidence limits, and a P-value the Cox Model will be used for this analysis. The analysis will be done using logrank test with the only variable included will be randomised treatment.

The Cox proportional hazard models will be fitted using the STATA's "sts cox" command. The baseline covariates will be included in the models. The results will be presented in terms of estimated Hazard Ratios with associated 2-sided 95% Confidence Intervals (CI) and P-value. The assumptions of proportional hazards will be assessed for each covariate using Schoenfeld residuals. Parallel lines indicate that the assumptions of proportional hazards are valid. In addition, the assumption of proportionality for each covariate will also be investigated with time-dependent explanatory variables to allow for an increasing (decreasing) trend in the hazard ratio over time. If the p-value from the Wald chi-squared statistic for a time dependent variable is less than 5%, there is evidence of a departure from the model assumptions.

Clinical events
Adverse events will be classified on the basis of MedRA terminology and summarised for each treatment. Adverse event incidence rates will be summarised by system organ class, preferred term, and severity of the adverse event (for pre-defined adverse events only). Each woman will be counted only once within a system organ class or a preferred term by using the adverse events with the highest severity within each category. The incidence of each adverse events will be summarised by treatment received and the formal statistical analysis will be performed using logistic regression with only treatment group as a factor. For each treatment comparison, the results from each test will be presented as the Odds Ratios (ORs), and the associated 95% confidence interval and P-value. The number and percentage of women experiencing any adverse event will be summarised by treatment randomised.

Mortality

The total number and percentage of women who die for any reason will be summarised by treatment allocated. Deaths will be summarised by main cause (i.e., from breast cancer or other causes). Deaths during treatment include all deaths occurring during treatment. For patients who die from a main cause other than breast cancer, deaths will also be summarised separately.

DCIS

Primary/secondary objectives

The log rank test will be used as the primary analysis to provide an unadjusted comparison of treatment groups for the superiority analysis. Cox proportional hazard models, adjusting for the baseline covariates, and will provide a hazard ratio with a corresponding confidence interval and p-value. A Kaplan-Meier plot will be produced showing the cumulative incidence of all breast cancers by time since randomization by treatment group. A forest plot will also be produced, showing the hazard ratios for each grade (low, intermediate, high), tumour size (≤10mm, 10-20mm, >20mm), age (≤60, >60), BMI (<25, 25-30, ≥30) and previous HRT use (never, previous, current). For the secondary analyses, no adjustment will be carried out to allow for sequential or multiple testing. To compare the effectiveness of tamoxifen and anastrozole according to the receptor status of the primary or recurrent cancer: Cox proportional hazard models, adjusting for the baseline covariates, will be fitted for each receptor status (ER-positive/ER-negative). To examine the rate of breast cancer recurrence and new contralateral tumours after cessation of tamoxifen or anastrozole: Cox proportional hazard models, adjusting for the baseline covariates, will be fitted. To examine the effect of tamoxifen vs anastrozole on breast cancer mortality: Cox proportional hazard models, adjusting for the baseline covariates. To examine the effect of tamoxifen and anastrozole on other cancers, cardiovascular disease, fracture rates, and non-breast cancer deaths: descriptive analyses will be produced for each of these outcomes other than non-breast cancer deaths, giving rates of each events by treatment, and calculating risk ratios and 95% confidence intervals using a generalized linear model with binomial family and log link function. For the outcome non-breast-cancer deaths, Cox proportional hazard models, adjusting for the baseline covariates.

Clinical events

Clinical events will be classified based on MedRA (Medical Dictionary for Regulatory Activities) terminology and summarised for each treatment. Clinical event incidence rates will be summarised by system organ class, preferred term (MedRA coding system), and severity of the clinical event (for pre-defined clinical events only). Each woman will be counted only once within a system organ class or a preferred term by using the clinical event with the highest severity within each category. The incidence of each of the clinical events will be summarised by treatment received and the formal statistical analysis will be performed using logistic regression with only treatment group as a factor (using Stata's "logistic" command). For each treatment comparison, the results from each test will be presented as the odds ratios (ORs), and the associated 95% confidence interval and p-value. The number and percentage of women

experiencing any pre-defined or common (more than 5%) side effect, or any with a significant difference between treatment arms ($p<0.02$) during the trial period will be summarised by treatment.

Mortality
The total number and percentage of women who die for any reason will be reported by treatment allocated. Deaths are reported by main cause (i.e., from breast cancer or other cause). For patients who die from a main cause other than breast cancer, deaths will also be reported separately.

11. Ethics

11.1. NHS REC reviewed research

This protocol has been approved by the HRA/REC. Approval was given from the London Fulham Research Ethics Committee 19/LO/0984

There is no immediate benefit or burden to UK participants as data is collected via data registries already. Direct contact with participants is not required for the IBIS-II-O study apart from newsletters and results updates.

This study has section 251 CAG approval (REF WHEN KNOWN) and additional consent will not be obtained for this cohort. The original aims and procedures outlined in the original patient information and consent forms of the CTIMP studies are considered consistent with the objective for IBIS-II-O and procedures outlined in the original patient information and consent form. As the cohort is already determined in this study there is no need for active screening and recruitment of participants.

Participants will be informed of their continuing participation in this study by means via the study newsletter. If they wish to opt out of continued data tracking and collection, they will be given clear instructions in the letter as to how they can do this (section 6.3). Further newsletter and communications will be provided for the duration of the study.

All participants have been informed by the local site of QMUL's legal obligations as data controller to adhere to the General Data Protection Regulation (GDPR) and informed of how their data will be processed and used as part of their ongoing participation in the main CTIMP studies. This same information was provided at site closure letter. Participants will be informed that their rights to access, change or move information are limited in order for the research to be reliable and accurate and if they withdraw from remote follow up, the research team will keep the information already obtained but will use the minimum personally-identifiable information possible.

11.2. Europe/Rest of World

For non-UK participants, ethical considerations will be dealt by the relevant local or national Ethics committees. The PI must submit this protocol for independent review by a recognised Ethics Committee. This committee should comprise medical professional and non-medical members in accordance with the local guidelines. The committee should be experienced in reviewing study protocols.

Data collection must not start until satisfactory evidence of Ethics Committee approval is given to the IBIS-II-O CCO. This written evidence should clearly identify the study and, where possible, the identity and occupation of the members of the committee that reviewed the protocol. Data will not be accepted by the IBIS-II-O coordinators if the site cannot provide evidence of local submission of the protocol or equivalent document and subsequent ethical approval.

A copy of this protocol can be used as a template by the participating site.

11.3. Annual Safety Reporting (APR)

The APR will be written by the CI (using HRA template) and submitted to the sponsor for review prior to submission to the REC. The APR is due within 30 days of the anniversary date of the “favourable opinion” letter from the REC.

12. Public involvement

The IBIS-II-O study design, patient letter, and the consent procedure were discussed with the Queen Mary Trial Advisory Group (QMTAG). This group will also review any patient facing materials throughout the course of the study. Their advice will be used to further guide the design of the study and study materials and results dissemination.

13. Data handling and record keeping

A study specific data management plan (DMP) outlines all relevant detail and is separate from this protocol.

13.1. Data management

Data from IBIS-II-O will be held on a separate Oracle table from the main IBIS-II CTIMP dataset so data provenance and a full audit trail can be maintained. The data will be processed to identify new events of interest and will be integrated into the existing IBIS-II participant dataset for analysis.

The IBIS-II CCO will acquire data for the study once a year via approved applications with NHS Digital, Public Health England, Northern Ireland Cancer Registry (NICR), NHS-Wales Informatics Service (NWIS) and the National Services Scotland.

The IBIS-II Central Coordinating Office (CCO) will send the participant cohort i.e., a list of participants with identifiable data (including full name, date of birth, postcode) to the digital registries. The data registries will return to QMUL, SNO linked data sets relating to cancer occurrence, death, and tumour-specific information. The returned data sets will be entered/uploaded into the IBIS-II study database, which already contains participant study data. Events of interest are verified by the GP if sufficient registry data is not available.

The IBIS-II-O DMP describes the procedures for comparison and integration of the IBIS-II database (Prevention and DCIS) with data received from the national registries.

The application process to request data from the digital registries are structured to promote compliance with the Data Protection Principles and Information Governance safeguards. Information Governance training is an application requirement and the institutions Information Governance Toolkit score will be supplied for security assurance.

Data will be collected and stored, as part of the IBIS-II-O study, in accordance with GCP, Information Governance guidelines and Bart's Cancer Centre Information Security Policy. The IBIS-II data is stored in an Oracle database and all changes to the data are audit logged. Excerpts and other trial information will be stored on the shared network drive in access-restricted folders.

All systems are protected by a multi-level approach involving firewall, router configuration, e-mail scanning and virus protection on all workstations on the Centre's network in addition to those measures taken by QMUL. All workstations have appropriate anti-virus software installed by BCC IT and is set up to update anti-virus signatures automatically.

13.2. Source Data

Table 10. Source data for IBIS-II-O

Source data item	Use	PID	Maintained
1. NHS-Digital, NWIS, NSS, NICR dataset	Identification of new breast cancers, deaths, and events of clinical significance from UK participants.	Yes	On a self-contained server on the BCC network which meets security requirements, as per DARS Guidance Notes on Security
2. Public Health England datasets	Validation of new and recurrent breast cancers.	No	On a self-contained server on the BCC network
3. Pathology reports for new breast cancers	Validation of new breast cancers where PHE data is insufficient	No	Paperwork filed in locked cabinet and archived at end of study, maintained by data custodian Jack Cuzick
4. Documentation and communication provided by participants GP	Validation of new deaths, breast cancers and events of clinical significance	Yes	Paperwork filed in locked cabinet and archived at end of study, maintained by data custodian Jack Cuzick
5. Datasets sent by PI for international sites.	Identification of new breast cancers, deaths, and events of clinical significance	No	Specified in DSA
6. Spontaneous reports of new or recurrent breast cancers and deaths	Local PI of previously closed site	No	Ad hoc

13.3. Confidentiality

The IBIS-II team will uphold the confidentiality of patients taking part in this study. PID will not be shared with any third parties and will not be used to contact the participant directly.

Information related to participants will be kept confidential and managed in accordance with the Data Protection Act, the General Data Protection Regulation (GDPR), NHS Caldicott Principles, the UK Policy Framework for Health and Social Care Research, and the conditions of Research Ethics Committee favourable opinion.

Encrypted patient identifiable data for UK participants will be securely stored at the IBIS-II CCO solely for the purposes of long-term follow-up via flagging and data linkage as outlined in secondary outcomes in full accordance with applicable regulations.

Identifiable and potentially identifiable data will be minimised to the extent possible while still ensuring end-points can be successfully met and these identifiers will be

removed when they are not required for a particular stage of processing. Any data for publication or distribution will fully anonymous.

As outlined in the informed consent documents signed for the main CTIMP studies, the CCO will contact the participants' GP when further information is required. In order to do this effectively and with assurance of the participant's consent, the CCO stores copies of the consent forms securely on site.

13.4. Access to data

Only delegated members of staff will be given access to the IBIS-II datasets.

13.5. Data Protection, Data storage and transfer

The original 'raw' data sets returned by data registries containing identifiable data will be stored on a separate server meeting enhanced security requirements in accordance with the providers data sharing agreement. Personal identifiable data are stored on the secure network and never on the local drives of unencrypted QMUL desktop PCs. The data will be pseudonymised before being provided to the study team on the Barts Cancer Centre Network.

The separate server for raw registry data is self-contained within the Barts Cancer Centre network, within the QMUL network. It is firewalled from external connections and the rest of the network. All traffic through the checkpoint firewall is logged. The perimeter defence firewalls protecting the national registry data are ITSEC E3 or Common Criteria EAL4 or Protected Profile (EAL4 Equivalent) compliant.

Trial data collected for the purposes of the IBIS-II O study will be stored in Oracle tables. The database will be stored and managed in an Oracle Database 11g Enterprise Edition on the Barts Cancer Centre network. QMUL creates back-ups of this data stored on its network and the encrypted backup tapes are stored offsite with Iron Mountain UK Ltd, Powergate Business Park, NW10 6PW (ISO 14001 and ISO 9001). The data is not accessible by any Iron Mountain employee.

13.6. Record retention and archiving

During the course of the research, all records are the responsibility of the Chief Investigator, and must be kept in secure conditions. When the trial is complete, it is a requirement of the UK Policy Framework for Social Care and Health Research and Queen Mary University of London that study records are kept for a minimum of 20 years. However, to ensure the continued association between the Prevention (EudraCT 2004-003991-12/MREC 02/8/70) and DCIS (EudraCT 2004-003992-35/MREC 02/8/71) CTIMP trials this protocol, all IBIS-O data and associated records will be stored for a minimum of 25 years from the CTIMP study end of trial definition in 2022 alongside the Prevention and DCIS TMF.

QMUL will provide an approved repository for the long-term storage of all the data and documentation related to the study. All research documentation will be archived in accordance with the sponsors requirements and SOPs.

The 'raw' data sets will be stored until the data destruction date as per the Agreements with the national registries. The storage architecture is compliant with the NHS DIGITAL/NWIS/NSS/NICR and PHE contracts. Once QMUL is issued with a Data Destruction notice, data from all storage including backups is securely and permanently removed within 14 days. Data can be securely wiped to NHS Digital standards (multi pass pattern wiped to at least HMG S5 Enhanced on site and if end of life, degaussed and physically destroyed).

Processed data sets with all identifiers removed except the Study ID will be retained for analysis until study completion, following which it will be archived for 20 years.

14. Safety reporting

Adverse events and side effect data

Information on specific clinical events (as described in the secondary and exploratory endpoints) will be collected as part of this observational study.

As this protocol concerns the long term follow up of participants that have already completed their trial treatment and the safety profiles of the trial therapies (anastrozole and tamoxifen) are well established, serious adverse events (SAEs) will not be collected nor reported in this study. Specific clinical events as listed within the trial objectives will still be reported within trial outputs. There are no procedures related to this protocol other than data collection.

15. Monitoring and auditing

This is an observational study with no direct patient contact, no active clinical research sites and therefore no on-site monitoring is required in the UK. Safety issues do not need to be considered in this study. Clinical events identified from data collection procedures will have already been managed locally by usual care. International sites will specify monitoring and validation procedures in the DSA.

Monitoring will be performed as per the study-monitoring plan will utilise central and statistical monitoring methods to ensure the data is accurate and of good quality.

The data collected will be integrated into prepared tables with minimal manipulation. Specific tests will be implemented periodically to ensure data integrity according to the trial specific data management plan. All procedures to manage the study database will be set up to ensure full compliance with GCP and national research governance requirements.

The Sponsor or delegate retains the right to audit any study, study site or central facility. In addition, any part of the study may be audited by the funders where applicable.

16. Study committees

The existing IBIS-II Prevention and DCIS trials independent TSC listed below will maintain oversight for this protocol given that they have the same primary outcomes. Long-term follow-up data from the continuing international CTIMP participants will be analysed in conjunction with data from this study.

Independent Trial Steering Committee:

Dr Richard Sainsbury (**Chair**, Independent member)
Dr Judy Garber (Independent member)
Professor Peter Sasieni (Independent member)
Prof Tony Howell (Chief Investigator, Non-independent member)
Prof Jack Cuzick (Observer)
Prof Nick Zdenkowski (Observer)
Dr Ivana Sestak (Trial Statistician, Observer)

The TSC meet annually to assess progress and review data progress from the main IBIS-II CTIMP protocols as specified in the IBIS-II TSC charter. The data from this protocol will be integrated with the main IBIS-II dataset and therefore monitored by the IBIS-II TSC until 2022. After the CTIMP closes, the IBIS-II the TMG should continue to provide oversight until the end of the study.

Independent Trial Management Committee:

Prof Jack Cuzick
Dr Ivana Sestak (Trial Statistician)
IBIS-II Trial Manager/Coordinator

The TMG will meet at least every 3 months

17. Finance and funding

AZ Educational Grant

18. Insurance and indemnity

The insurance that Queen Mary University of London has in place provides cover for the design and management of the study as well as "No Fault Compensation" for

participants, which provides an indemnity to participants for negligent and non-negligent harm.

19. Dissemination of research findings

Results will be published in high impact, peer reviewed open access scientific journals accessible to the research community and the general public. The sponsor will be acknowledged in all publications and dissemination of results. Through newsletters and the trial website, the trial team will aim to continue to keep participants aware of trial outputs and work with PPI representatives to communicate the results appropriately.

20. References

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This protocol is based on JRMO Protocol template for Research Studies; version 1.0, February 2018.

21. Appendices

21.1. Exclusion/inclusion criteria for IBIS-II Prevention and DCIS

IBIS-II Prevention - Inclusion Criteria

Entry criteria will be age-dependent to reflect increasing baseline risk with age;

Women aged 45-70

The entry criteria are based on a relative risk of at least two-fold and are similar to those in IBIS-I.

At least one of the following must be satisfied:

1) First degree relative who developed breast cancer at age 50 or less
2) First degree relative who developed bilateral breast cancer

Two or more first or second-degree relatives who developed breast or ovarian cancer. If both relatives are second degree and on opposite sides of the family, then at least one must have been diagnosed at age 50 or less

Nulliparous (or first birth at age 30 or above) and a first degree relative who developed breast cancer

5) Benign biopsy with proliferative disease and a first degree relative who developed breast cancer

Mammographic opacity covering at least 50% of the breast in absence of HRT use within the last 3 months. Either films or digitised images must be verified by a designated national radiologist or by someone that has undertaken the mammographic density training set for confirmation of eligibility prior to randomisation.

Also women aged 60-70

Because of their higher baseline risk, women aged 60-70 can enter the study with a smaller relative risk (approximately 1.5 or greater). This corresponds to a similar 5-year absolute risk as that for a 50-year old woman in the above group (approximately 3% at 5 years). These women need only have one or more of the following risk factors:

First degree relative with breast cancer at any age

Age at menopause $\geq$ 55 years

Nulliparous or age at first birth 30 years or above

Women aged 40-44

Women aged 40-44 who are postmenopausal (usually because of a bilateral oophorectomy) are eligible if they satisfy one or more of the following criteria (approximately 4-fold risk or greater):

Two or more first or second-degree relatives who developed breast or ovarian cancer at age 50 or less

First degree relative with bilateral breast cancer who developed the first breast cancer at age 50 or less

Nulliparous (or first birth at age 30 or above) and a first degree relative who developed breast cancer at age 40 or less

Benign biopsy with proliferative disease and a first degree relative who developed breast cancer at age 40 or less

All Age Groups (40–70) – women who have had certain breast conditions will also be eligible. These are:

Lobular carcinoma in situ (LCIS)
Atypical ductal or lobular hyperplasia in a benign lesion
Ductal carcinoma in-situ (DCIS), treated by mastectomy within the last 6 months, Oestrogen Receptor or Progesterone Receptor status, (ER or PgR), of DCIS must be known, and must be greater than or equal to 5% positive cells. This is equivalent to a Quick score of 3 or above and an H-score of 10 or above. Quick scores and H-scores must be given as whole numbers. DCIS patients treated by mastectomy with single or multiple focus of microinvasion (<1mm) are eligible for the Prevention trial. An extension of up to a further 3 months may be obtained for this eligibility criterion with prior approval from one of the IBIS II Steering Group co-chairmen.
Women with a ten year risk greater than 5%, who do not fit into the above categories (risk equivalent). All risk equivalent women must be approved by the Steering Committee Co-Chairman (London IBIS central office). These women must have clearly apparent family history and/or other risk factors indicating appropriate increased risk of breast cancer for their age. Particularly careful assessment of the risk-benefit for these women should be undertaken before a woman from this group is entered.

IBIS-II Prevention - Exclusion Criteria

Premenopausal women.
Any previous diagnosis of breast cancer (including DCIS excised >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 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.
e) Intention to continue to use oestrogen-based hormone replacement therapy (HRT).
f) Women who have either had a prophylactic mastectomy or are planning to have this procedure.
g) Evidence of osteoporosis* or low trauma vertebral fractures within the spine. However, these women may be eligible if their T-score is greater than or equal to minus four, and if they have no more than two low trauma vertebral fractures. In either case they must be managed in accordance with local clinical procedures for treatment of such women ie take bisphosphonate treatment and have regular DXA scans. Women with T-scores less than minus four, or with more than two low trauma vertebral fractures are not eligible.

* The WHO definition of osteoporosis is a T-score of -2.5 or less at the femoral neck. However, it is recommended that a T-score of -2.5 or less at the lumbar spine should also be considered as osteoporotic in terms of all IBIS-II protocols.

h) 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. Reference should be made to the appropriate Summary of Product Characteristics (SmPC).

i) Life expectancy of less than 10 years or other medical condition that would significantly interfere with the ability to accept the chemo-preventive treatments.

j) Psychologically and physically unsuitable for five years anti-oestrogen therapy.

k) Treatment with non-approved or experimental drug during the 6 months before randomisation.

l) History of gluten and/or lactose 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, e.g. 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 progestagens and tibolone are contra-indicated for women at increased risk of breast cancer. Please note that this is not an exclusion criterion for IBIS-II but women should be made aware of this risk and a clinical decision should be made as to inclusion on the trial.
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.

IBIS-II DCIS - Inclusion Criteria

All women must be postmenopausal and between the ages of 40-70. In certain circumstances women who are within 24 months of this age range may join the trial by obtaining prior approval from one of the IBIS-II steering group co-chairmen. Postmenopausal status is defined as meeting one or more of the following criteria:

7. over the age of 60
8. bilateral oophorectomy
9. aged ≤ 60 with a uterus and amenorrhoea for at least 12 months
10. aged ≤ 60 without a uterus and with FSH >30 IU/L NB If participant is taking HRT, an 8 week wash-out period is required prior to FSH test being performed.

11. Participants who have had surgery to remove a DCIS 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 or equal to 5% positive cells. This is equivalent to a Quick score of 3 or above and an H-score of 10 or above. Quick scores and H-scores must be given as whole numbers.
12. Participants who have been diagnosed with atypical hyperplasia or lobular carcinoma in situ at any time.
13. 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. Two spinal x-rays in one lateral dimension will also be required to rule out low trauma vertebral fractures.
14. Fully informed signed consent must have been obtained.
15. Participants who took part in IBIS-I but have been off trial therapy for at least 5 years.

IBIS-II DCIS - Exclusion Criteria

1. Premenopausal women.
2. Any previous diagnosis of breast cancer (including DCIS excised >6 months ago)
3. Any other previous cancer in the past 5 years (except non-melanoma skin cancer or in situ cancer of the cervix)
4. Current treatment with anti-coagulants.
5. Previous deep vein thrombosis or pulmonary embolus.
6. Previous transient ischaemic attack (TIA) or cerebrovascular accident (CVA, stroke).
7. 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.
8. Intention to continue to use oestrogen-based hormone replacement therapy (HRT).
9. Women who have either had a prophylactic mastectomy or are planning to have this procedure.
10. Any woman with unexplained postmenopausal bleeding.
11. Evidence of osteoporosis* or low trauma vertebral fractures within the spine. However, these women may be eligible if their T-score is greater than or equal to minus four and they have no more than two low trauma vertebral fractures. In either case they must be managed in accordance with local clinical procedures for treatment of such women ie take bisphosphonate treatment and have regular DXA scans. Women with T-scores of less than minus four or with more than two low trauma vertebral fractures are not eligible.
12. The WHO definition of osteoporosis is a T-score of -2.5 or less at the femoral neck. However, it is recommended that a T-score of -2.5 or less at the lumbar spine should also be considered as osteoporotic in terms of all IBIS-II protocols.

13. 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. Reference should be made to the appropriate Summary of Product Characteristics (SmPC).
14. Life expectancy of less than 10 years or other medical condition which would significantly interfere with the ability to accept the chemo-preventive treatments.
15. Psychologically and physically unsuitable for five years anti-oestrogen therapy.
16. Treatment with non-approved or experimental drug during the 6 months before randomisation.
17. History of gluten and/or lactose intolerance.

21.2. Data Sharing Agreement minimum specifications for international sites

1. Consent procedure/process
2. Verification/validation of clinical events
3. What clinical events will be collected?
4. Availability of pathology for new events
5. Frequency of data exports
6. Method of data collection
7. Delegation of duties
8. Data protection
9. Approval dates
10. Key documents – Version and Date