CLOCS

Cancer Loyalty Card Study

Version 3 06/05/2020

MAIN SPONSOR: Imperial College London
FUNDERS: Cancer Research UK
STUDY COORDINATION CENTRE: **Ovarian Cancer Action Research Centre**
Imperial College London
4th Floor, Institute of Reproductive and Developmental Biology (IRDB)
IRAS Project ID: 262776

Protocol authorised by:

Name & Role	Date	Signature
James Flanagan, Principal Investigator	08/08/2019	
Hannah Brewer, Research Associate	08/08/2019	

Study Management Group

Chief Investigator: James Flanagan

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Statistician: Marc Chadeau-Hyam

Study Management: James Flanagan

Study Coordination Centre

For general queries, supply of study documentation, and collection of data, please contact:

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Registration:
E-mail: clocs@imperial.ac.uk
Web address: clocsproject.org.uk

A list of research sites where recruitment will take place in the clinic can be found in Appendix 3.

Clinical Queries

Clinical queries should be directed to James Flanagan who will direct the query to the appropriate person.

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office
Imperial College London and Imperial College Healthcare NHS Trust
Room 215, Level 2, Medical School Building
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Funder

Cancer Research UK Early Diagnosis Project Grant (C38463/A26726)

This protocol describes the Cancer Loyalty Card study (CLOCS) and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

CLOCS	Cancer Loyalty Card Study
HSR1	High Street Retailer 1
HSR2	High Street Retailer 2

KEYWORDS

Ovarian Cancer
Epidemiology
Observational Study
Risk Assessment

STUDY SUMMARY

TITLE Cancer Loyalty Card Study (CLOCS)

DESIGN Observational, retrospective case-control study

AIMS The CLOCS aims to investigate whether or not women have distinctive self-management behaviours prior to seeing their doctor with symptoms that are associated with ovarian cancer.

OUTCOME MEASURES The primary outcome of the CLOCS will be to define the time by which the cases and controls are statistically significantly different in their purchase behaviours leading up to diagnosis on a population level.

The secondary outcome of the CLOCS will be defining a purchase threshold as an "alert" about cancer symptoms in individuals and determining the predictive utility of purchasing behaviours in the early detection of ovarian cancer. Exploratory analyses will include longitudinal analyses, frequency of purchases and an unbiased analysis of other purchase categories.

POPULATION At least 1000 women in the UK (500 ovarian cancer cases and 500 controls)

ELIGIBILITY Women, at least 18 years old, who own at least one participating high street retailer loyalty card are eligible to join the CLOCS. Among these women, those who have been diagnosed with ovarian cancer can join the CLOCS as cases, and those who have no prior ovarian cancer diagnosis are eligible to join as controls.

DURATION 3 years

1. INTRODUCTION

1.1 BACKGROUND

The ten-year survival rate for epithelial ovarian cancer (EOC) is only 35% in the UK and is dramatically different for stage 1 disease (90%) compared with stage 3-4 (5-15%). Survival in the UK lags behind Europe; this is attributed partly to a delay in diagnosis [1]. Earlier detection of low-volume disease or earlier stage ovarian cancer will save lives [2].

EOC is a heterogeneous disease with different histological subtypes that show strikingly different molecular [3] and mutational profiles [4,5]. With the Ovarian

Cancer Association Consortium (OCAC), we have identified 34 common genetic polymorphisms contributing to polygenic risk [6–9]. Epidemiological risk factors provide a predictive model with a modest discriminatory power (AUC=0.65), improved slightly with polygenic risk (AUC=0.66) [10], and this model has been proposed to improve EOC detection with risk stratified screening [11].

EOC usually presents with vague and non-alarming symptoms. As a result, most women are diagnosed late when the cancer has already spread and the prognosis is poor. The most common symptoms associated with EOC are increased abdominal size, pelvic pain, abdominal pain and bloating, feeling full quickly and difficulty eating [12,13]. The major reasons for not presenting to the GP with symptoms such as these are “not wanting to waste the GP’s time” [14] and normalisation of these symptoms [15]. The persistence of a symptom, social influence and awareness encourage help-seeking behaviours in primary care [16]. However, few believe that their symptom(s) might be a sign of cancer [17]. Consequently, people might choose to self-manage their symptoms by using over-the-counter medication, and to seek advice from other sources, (pharmacists, family, internet), rather than a primary care physician.

1.2 RATIONALE FOR CURRENT STUDY

Approximately 7,400 new cases of ovarian cancer are diagnosed each year in the UK, and with over 4,000 women dying from the disease each year it is a particularly lethal form of cancer. The symptoms are not well known, are vague and non-specific and most women are diagnosed at a late stage when the cancer has already spread around the peritoneum with poor prognosis. Novel methods are needed to improve earlier detection and thereby improve survival from this disease. We hypothesise that a change in purchasing behaviour, primarily an increase in self-medication to treat these vague cancer symptoms, may provide a novel avenue for earlier diagnosis for cancer.

In this study we propose to use loyalty card data from two participating high street retailers (Boots and Tesco) to investigate purchase behaviour as an opportunity for cancer symptom surveillance. We aim to conduct a case-control study of women with ovarian cancer (cases) matched with women who do not have ovarian cancer (controls) and define the time by which the cases are statistically significantly different in their purchase behaviours leading up to date of diagnosis, compared with the control purchase behaviours.

2. STUDY OBJECTIVES

2.1 The primary aim of the CLOCS will be to define the time by which participants with ovarian cancer are statistically significantly different in their purchase behaviours leading up to date of diagnosis, compared with purchase behaviours of participants without ovarian cancer.

2.2 The secondary aim of the CLOCS will be to define a purchase threshold as an “alert” about cancer symptoms in individuals and determining the predictive utility of purchasing behaviours in the early detection of ovarian cancer.

3. STUDY DESIGN

Purpose and Design

The Cancer Loyalty Card Study (CLOCS) is addressing whether or not data already collected by high street retailers can detect significant changes in purchase behaviours of ovarian cancer patients prior to their diagnosis. We aim to conduct a case-control study of ovarian cancer patients matched with women who do not have ovarian cancer. We will recruit at least 500 recently diagnosed ovarian cancer patients and at least 500 healthy women as controls and collate up to 6 years of prior purchase data.

Recruitment
Women living with ovarian cancer and who own at least one of the participating high street retailer's loyalty cards will be recruited in a clinic by a member of their healthcare team where the study is open (recruitment sites listed in Part C).

Women, 18 years or older, living in the UK who have a loyalty card at the participating high street retailers will be recruited through the study website (www.clocsproject.org.uk) where data collection will be safeguarded using an encrypted web form that includes study consent and the self-report questionnaire. There will be a press release and social media about the study inviting loyalty card holders to visit the CLOCS website for more information and join the study. Any woman considering joining the study can contact the research team using the contact details on the information sheet.

Consent
Ovarian cancer patients will be given the information sheet and consent form in the clinic by a member of their healthcare team. They can take as much time as they need to read through the information sheet. If they choose to participate, they can complete the consent form whenever is convenient for them and return it to the CLOCS team in the freepost envelope provided to them in the clinic.

Alternative recruitment strategy during Covid-19 lockdown to minimise contact with patients
The research sites will be asked to identify the patients who may be eligible for the study using their records and contact them by phone to facilitate recruitment to CLOCS. During this process, the research nurse will read out the information sheet and ask participants if they wish to take part. If patients are interested in taking part, then they will complete the consent forms and the questionnaire on their behalf. They will take a copy of the completed questionnaire and the consent form and post the original to the CLOCS team using CLOCS freepost envelope and post the copy including the information sheet and privacy policy to the patients. Patients similar to the previous protocol can withdraw their consent at any stage of the study.

Women without ovarian cancer will be presented with the information sheet and consent form on the study website and can consent to participate online.

Methods
Consenting participants will complete a brief questionnaire about ovarian cancer risk factors, which will also be returned to the CLOCS team through the mail or on the website (healthy volunteers only). Participants with ovarian cancer will also have a clinical form for a member of their clinical team to complete in the clinic. This will be sent to the CLOCS team along with their consent and risk factor questionnaire in the freepost envelope. In order to adhere with participating high street retailers' policies, healthy volunteers will need to provide a photo ID and utility bill for ID verification. This is not required for participants with ovarian cancer because they will be recruited by a member of their care team in the clinic.

Two ovarian cancer patients have reviewed all questionnaires and CLOCS documents and expressed their approval. Women without ovarian cancer from the general UK population have also reviewed the risk factor questionnaire and expressed their approval saying the questionnaire is 'easy to understand' and 'straightforward'.

If participants consent to be re-contacted by the CLOCS team for future studies or for loyalty card detail clarification, they will provide either a contact email or phone number. There is no further action needed from participants once they complete their consent form and questionnaire (and clarify loyalty card details if necessary).

3.1 STUDY OUTCOME MEASURES

We aim to detect significant changes in purchase behaviours of ovarian cancer patients prior to diagnosis, and potentially improve the sensitivity of detection of cancer "alert symptoms" by stratifying the analysis on risk profiles, cancer stage or histology.

4. PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

No tests need to be done before patient entry to the study.

4.2 INCLUSION CRITERIA

Women, at least 18 years old, recently diagnosed and living with ovarian cancer (all ovarian and peritoneal cancer diagnoses will be eligible),preferably recruited just after diagnosis and during treatment period but are still eligible if diagnosed up to 2 years prior, at the latest, who hold at least one participating high street retailer loyalty card are eligible to join the CLOCS as cases.

Women, at least 18 years old, who have not been diagnosed with ovarian cancer and hold at least one participating high street retailer loyalty card are eligible to join the CLOCS as controls.

4.3 EXCLUSION CRITERIA

Women under the age of 18 years and, since this is a study about ovarian cancer, men will not be eligible to join this study.

4.4 WITHDRAWAL CRITERIA

If at any point, a CLOCS participant wishes to withdraw her participation, she can email the CLOCS research team at clocs@imperial.ac.uk expressing her desire to withdraw consent.

The CLOCS team will then delete that participant's information from the CLOCS database.

5. PARTICIPANT RECRUITMENT AND CONSENT

The CLOCS will recruit loyalty card holders through advertisement of the study and through clinics around the UK where the CLOCS is open. Advertisement of the CLOCS will start with a press release introducing the study to the general population, inviting loyalty card holders to visit the CLOCS website for more information and possibly participate.

5.1 RECRUITMENT OF WOMEN WITHOUT OVARIAN CANCER (CONTROLS)

Women without ovarian cancer will be recruited through the study website (www.clocsproject.org.uk) where data collection will be safeguarded using an encrypted web form that includes study consent and the self-report questionnaire. No clinical questionnaire is needed for control participants.

The online participation will take up to 15 minutes and data will be transferred immediately to the secure CLOCS server. The website approach was adopted as one of the outcomes of the proof-of-concept study. It aims to provide a transparent environment where potential participants can make informed decisions about participation in CLOCS, and the data risks are minimised using encryption. We have carefully designed the website to inform the general public about how we will process their data in CLOCS, how they can withdraw from the study if they wish to do so and use it as a platform to provide feedback as we progress in the larger CLOCS project. The research team will use several methods to recruit control participants to the study which will include a press release carried out by the project funders and the Imperial College London public engagement team, dissemination of study flyers and leaflets, and social media marketing techniques on Twitter and Facebook using paid advertisement and unpaid methods. The application of the social media recruitment methods will allow researchers to reach a larger cohort in the UK. The application of both paper-based and online recruitment methods will be carried out throughout CLOCS and will be recorded.

5.1.1 ID Verification

In order to adhere with participating high street retailers' policies on data portability, healthy volunteers are required to provide a photo ID in the form of a photo of their passport or drivers licence and a utility bill (e.g. council tax or electricity/gas bill) for ID verification. This is an added step to confirm that participants did not complete the survey on behalf of someone else and to ensure that our research is complaint with the GDPR. Based on this, This information will be stored and deleted as described in section 9.1.6a.

Control participants will be presented with a separate encrypted link for uploading their ID verification details once they consent to the study and complete the survey. If participants do not provide this data, we cannot retain their data or request their information from the retailers. To allow sufficient time to gather the necessary documents and doing it on their own time, we will be sending two reminders to the participants who agreed to the study and have given consent for ID verification. The first reminder will be sent 24 hours after the risk factor questionnaire submission, and a final reminder will be sent one week after the first reminder if the participant still has not completed the ID verification step. The copy of the verification page and the reminders are included in the appendices.

5.2 RECRUITMENT OF WOMEN WITH OVARIAN CANCER (CASES)

Women living with ovarian cancer and at least one loyalty card will be eligible to participate in this study. Ovarian cancer patients will first be approached by a member of their direct care team.

The member of the direct care team will discuss the study with the patients and give them the patient information sheet. They will be made aware that participation is voluntary and even if they do not want to participate it will not affect their care and treatment. They will also be made aware that they can withdraw at any time without affecting their usual care and treatment. Patients will be made aware they can take as much time as they need to decide on participation including discussing their participation with relatives and personal doctors. If they have any further questions that the member of the direct care team cannot answer, they will be encouraged to

contact the CLOCS team using the contact details included in the patient information sheet. The CLOCS team will be available to explain the study further and answer all questions. If they are willing to participate, they will then be given the consent form to sign and complete whenever is convenient for them and return to the study team using the freepost envelope.

5.3. RECRUITMENT CONTINGENCY PLAN (COVID-19 RESTRICTIONS)

5.3.1 During the COVID-19 pandemic, participating recruitment centres are consulting with patients over the phone and not seeing them in person. Where feasible, research nurses or clinicians will recruit patients using the following process:

1. Read through the information sheet and complete the consent form and questionnaires with patient on the phone.
2. Make a copy of the information sheet and completed forms and post them to the patient who chose to take part in CLOCS. This would include a cover letter provided by the CLOCS team.
3. Post the original completed forms to the CLOCS team using the CLOCS Freepost name (Freepost CLOCS PROJECT).

5.3.2 Recruitment for controls will remain on the CLOCS website.

5.4 Any queries from potential participants about joining and participating in the CLOCS will be answered by the research team via the CLOCS email address: clocs@imperial.ac.uk.

5.5 Upon choosing to participate, women will complete a consent form to participate in the CLOCS and return it to the study team either via mail or the CLOCS website (controls only), giving permission to the CLOCS team to request access to and analyse loyalty card information from the participating high street retailers.

5.6 The consent form requests permission from the participants for the CLOCS research team to re-contact participants regarding their loyalty card details for verification or future related studies. If a participant consents to be contacted again by the CLOCS team, she will provide either a contact email address or phone number.

5.7 A member of the of ovarian cancer patient's clinical team can approach a patient who meets the study eligibility criteria, explain the study to the patient and let the patient know that participation is voluntary, and if the patient does not want to take part, it will not affect patient care.

5.8 Any participant can withdraw from the study at any time after consent without providing any reason.

6. OVARIAN CANCER RISK FACTOR AND SYMPTOM DATA COLLECTION

6.1 Upon choosing to participate in the CLOCS, participants will also complete a questionnaire requesting information about well-established ovarian cancer risk factors and symptoms.

6.1.1 The well-established risk factors include ethnicity, marital status, body mass index, age at menarche, menopausal status, age at menopause, parity,

breastfeeding, hysterectomy, tubal ligation, cancer history, endometriosis, aspirin use, oral contraceptive use, hormone replacement therapy (HRT), family history of ovarian and breast cancers, vaping, and cigarette smoking

6.1.2 The questionnaire asks participants about the symptoms experienced (if any) and number of visits to the general practitioner in the year leading up to cancer referral or diagnosis.

6.1.3 The questionnaire asks participants about which food and pharmacy stores they shop at regularly, at which stores they own a loyalty card, frequency of use of those loyalty cards, where they heard about the study (for controls only), and the number of people in their household (for adjustment in analysis).

6.1.4 In order to understand the impact of COVID-19 on purchase history and ovarian cancer diagnosis delays, the questionnaire includes a question about whether participants have had Covid19 (diagnosed and recovered/diagnosed and still ill/suspected but not formally diagnosed/did not have covid)

6.1.5 For participants diagnosed with ovarian cancer (considered cases), this will occur in the clinic or at home if they choose to complete it at home.

6.1.6 For participants who do not have ovarian cancer (considered controls), this questionnaire will be completed online.

6.2 For participants with ovarian cancer, there will be a separate questionnaire to be completed by their recruiting clinician or member of their healthcare team regarding information about ovarian cancer diagnosis date, type, grade, stage, and surgical outcome, if any. If a patient chooses to complete the questionnaire at home, a member of the clinical care team will send their completed clinical questionnaire with them.

6.3 The clinical care teams will not keep a copy of the CLOCS participant consent form.

6.4 The member of the clinical care team who recruits the patient in the clinic is responsible for reporting the number of patients recruited to CLOCS on their Local Portfolio Management System (LPMS), and a member of the CLOCS research team will confirm these reports on the Central Portfolio Management System (CPMS).

6.5 Once all relevant risk factor and symptom questionnaires are completed, they will be returned to the CLOCS research team either via mail or through the CLOCS website (controls only).

6.6 All questionnaire data will be entered into an encrypted database housed on the secure server at Imperial College London, linked only by the pseudonymised study barcode.

7. LOYALTY CARD DATA COLLECTION

7.1 The CLOCS team has discussed the study with the two participating high street retailers and data sharing agreements will be signed with them before any data is transferred between the study and the high street retailers.

7.2 Women who choose to voluntarily participate in the CLOCS will provide signed, informed consent for their loyalty card data from participating high street retailers to be shared with the CLOCS research team.

7.3 When the consent form is returned to the CLOCS research team, the CLOCS team will transfer the encrypted list of CLOCS participants and their loyalty card numbers to a secure Imperial College London file exchange that will be accessible to the high street retailer using a password. The completed paper consent form will be stored in a locked cabinet in a locked room in a building that requires a security badge to access.

7.4 The high street retailer will verify the participant information with their loyalty card data and will transfer the encrypted past purchase data back to the CLOCS research team using the secure Imperial College London file exchange.

7.5 If the participant's loyalty card details provided by the participant in the consent form does not match the high street retailer's records for that participant's name and the participant consented to be re-contacted, then the CLOCS research team will attempt to contact the participant to verify the card details.

7.5.1 CLOCS participants will only be re-contacted using their preferred method of contact they indicated in the consent form.

7.5.2 The CLOCS team aim to only re-contact participants as needed and will be mindful of participants' time and space.

7.6 If the participant's loyalty card details provided by the participant in the consent form do not match the high street retailer's records for that participant's name and the participant did not consent to be re-contacted, then the CLOCS research team will not be able to access the participant's loyalty card data and will exclude them from the study.

7.7 The date of recruitment as written on the questionnaire and consent forms will be the final date of purchase data requested by the CLOCS team. At most, up to 6 years of participants' past purchasing data prior to the date of recruitment will be shared with the CLOCS team, depending on the high street retailer's records and when the participant obtained the loyalty card. This includes data about the items purchased (e.g. paracetamol), when (i.e. date of purchase) and where they were purchased (i.e. store postcode). This will not include information on NHS prescriptions or any personally identifiable information, e.g. full name, postcode, ethnicity.

7.8 The CLOCS team will save the past purchase data to a secure and encrypted server based at Imperial College London.

8. ASSESSMENT AND FOLLOW-UP

CLOCS participants will only be re-contacted after joining to either confirm loyalty card details and ID verification or to contact participants about future studies related to the CLOCS, subject to their consent to be re-contacted.

The CLOCS is funded from 1 February 2019 to 1 February 2022, but risk factor and symptom data collected in this phase will be available for analysis for up to ten years after completion of the study. Past purchase history data will only be kept for five years or until the

results are published, whichever happens first. Then the purchase data will be completely anonymised and any link to identifiable data deleted.

9. STATISTICS AND DATA ANALYSIS

9.1 Data management and flow

9.1.1 All data will be stored and processed in the College's ISO27001 certified secure environment – the "Secure Enclave". This is a fully managed infrastructure and secure environment providing high availability, resilience and business continuity through multiple servers, back-ups and disaster recovery measures.

A robust data security model has been designed to protect sensitive personal and medical data from the potential risk of unauthorised access or distribution. All information input, viewed or extracted is be protected so that only users with the correct authority and access can create, view, amend or delete information. Access to the system will be governed by authentication and authorisation privileges that will check:

- Access is by an authorised person and the user is who they say they are. This is controlled by a username and complex password;
- The user accessing the system is authorised to do what they are attempting to do. That includes searching, updating, deleting and uploading information at the appropriate authorised level for the database(s) or table(s).

In summary, the security architecture provides the optimal level of protection available through implementing best practice network, hardware, software and data security measures.

9.1.2 All analysis data will be pseudonymised.

9.1.3 Past purchase data will be kept until the results are published or five years from the date of participation in CLOCS, whichever comes first. Then all past purchase data will be anonymised and any link to identifiable data will be deleted.

9.1.4 Ten years after the study is complete, all paper-based documents and electronically held identifiable data, including consent and contact details, will be destroyed or deleted in accordance with Imperial College London's data deletion and retention processes.

9.1.5 The CLOCS research team is committed to protecting the confidentiality of data. Systems have been established for the secure data flow and storage of data to protect confidentiality. All identifiable information, including contact details will remain secure at the research site. A master file, allowing re-identification and linkage will be managed by James Flanagan, the CLOCS chief investigator. The access to de-identified data within Imperial College will be limited to approved researchers.

9.1.6 Once completed consent forms, risk factor and symptom questionnaires, and clinical questionnaires (for cases) are returned to the CLOCS research team, all information will be entered onto the secure server. The encrypted list of consenting CLOCS participant names and loyalty card numbers for each

participating high street retailer will be transferred to participating high street retailer 1 (HSR1) and participating high street retailer 2 (HSR2) using a secure file exchange provided by Imperial College London. The file transfer will require a password to access what has been transferred. The flow of data is shown in Appendix 2.

HSR1 and HSR2 will never know the cancer status of participants nor their loyalty card status or details at the other HSR.

9.1.6a In accordance with the participating high street retailers' policies, healthy volunteers will need to provide a photo ID and utility bill for ID verification. These will be stored in the Secure Enclave, checked, and confirmed to match the details on the consent form. Once confirmed and the high street retailers have returned the purchase history, the photo ID and utility bill be deleted.

9.1.6b After two reminders, if we do not receive relevant information to confirm the identity of the participants, we will remove their consent and questionnaire data from our database and permanently delete their responses as they would be considered 'not validated' and we cannot request their data from HSR1 and HSR2.

9.1.7 HSR1 and HSR2 will verify participant loyalty card information, and will transfer encrypted participant past purchase data, linked only via the pseudonymised barcode id, back to the CLOCS research team, in line with the data sharing contracts.

9.1.8 The CLOCS research team will then save the encrypted participant purchase history data to the CLOCS secure server to be used for analysis.

9.2 Data analysis

9.2.1 The statistical software R will be used for all data analyses.

9.2.2 We will define the time prior to diagnosis by which the cases become statistically significantly different in their purchase behaviours to the controls.

9.2.3 We will explore this using a multivariable, conditional logistic regression model with ovarian cancer as the outcome and "purchase proportion" at different times prior to diagnosis as the exposure, adjusting for stage and histology and other potentially confounding variables collected from the risk factor questionnaire.

9.2.4 We will compare the proportions of purchases in cases to controls, stratified by risk quintiles defined by the epidemiological risk model (estimated n=86 per quintile) or by histology (with expected proportions of high grade serous cases n=335; mucinous cases n=70; endometriod n=35; clear cell n=35, and low grade serous n=25).

9.2.5 We will estimate the predictive values (ROC AUC, PPV, NPV, specificity and sensitivity) of this "early diagnosis" test for each stratum.

9.2.6 We will conduct exploratory analyses investigating other methods leveraging the auto correlation in the longitudinal data. Specifically, we will investigate the frequency of purchases and purchase trajectories, to identify purchase patterns (e.g. increasing purchases before diagnosis, purchase peaks, etc.), that are indicative/predictive of the individual disease onset.

9.2.7 Using longitudinal approaches, we will investigate if these patterns help in predicting the time-to-onset.

9.2.8 This type of approach could be generalised using other purchase categories for further hypothesis generation.

10. REGULATORY ISSUES

10.1 ETHICS APPROVAL

The Chief Investigator has obtained approval from the North West - Greater Manchester South Research Ethics Committee (19/NW/0427). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

10.2 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

10.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

Any CLOCS documents in paper form will be kept in a locked cupboard in a locked office within a locked department in the Imperial College main study site, and only the chief investigator will have access.

All data are kept in the Secure Enclaves, an isolated environment within Imperial College network. It is split into two main sections, one for holding identifiable data, and the other for de-identified research data. It was created to give Imperial College assurance that groups holding personal health data were compliant with all their processing requirements. All access into the enclaves is controlled and audited by the Security Manager and Quality Assurance Officer. The environment is Data Security and Protection Toolkit compliant and ISO27001 certified.

Data Handling and Security

The CLOCS research team is committed to protecting the confidentiality of data. Systems have been established for the secure data flow and storage of data to protect confidentiality. All identifiable information, including contact details will remain secure at the research site. A masterfile, allowing re-identification and linkage will be managed by James Flanagan, the CLOCS chief investigator. The access to de-identified data within Imperial College will be limited to approved researchers.

Secure Operating Environments
All data will be stored and processed in the College's ISO27001 certified secure environment – the "Secure Enclave". This is a fully managed infrastructure and secure environment providing high availability, resilience and business continuity through multiple servers, back-ups and disaster recovery measures.

A robust data security model has been designed to protect sensitive personal and medical data from the potential risk of unauthorised access or distribution. All information input, viewed or extracted is protected so that only users with the correct authority and access can create, view, amend or delete information. Access to the system will be governed by authentication and authorisation privileges that will check:

- Access is by an authorised person and the user is who they say they are. This is controlled by a username and complex password;
- The user accessing the system is authorised to do what they are attempting to do. That includes searching, updating, deleting and uploading information at the appropriate authorised level for the database(s) or table(s).

In summary, the security architecture provides the optimal level of protection available through implementing best practice network, hardware, software and data security measures.

Participant identity will be linked to the analysis datasets only through a unique barcode assigned when completing the recruitment questionnaire, meaning the data will be pseudonymised. The only identifiable information will be on the consent form along with the participant barcode. Retailer data and questionnaire data will only be linked via the pseudonymised participant barcode. The only person with access to the link between participant identity and the barcode is the chief investigator and this information will be kept in a locked cupboard (paper form) and on the secure encrypted server (electronic form). All researchers on the study team understand all data is confidential.

10.4 INDEMNITY
Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

10.5 SPONSOR
Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

10.6 FUNDING
Cancer Research UK are funding this study under the Cancer Research UK Early Diagnosis Project Grant (C38463/A26726).

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

11. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through the CLOCS research team.

12. PUBLICATION POLICY

At the end of the study, we aim to publish results of findings in peer-reviewed journals and present them at conferences. Extra care will be taken to ensure no participants are identifiable in any of the dissemination. The final study report will be produced summarising the information we have learned and will be hosted on the study website.

13. REFERENCES

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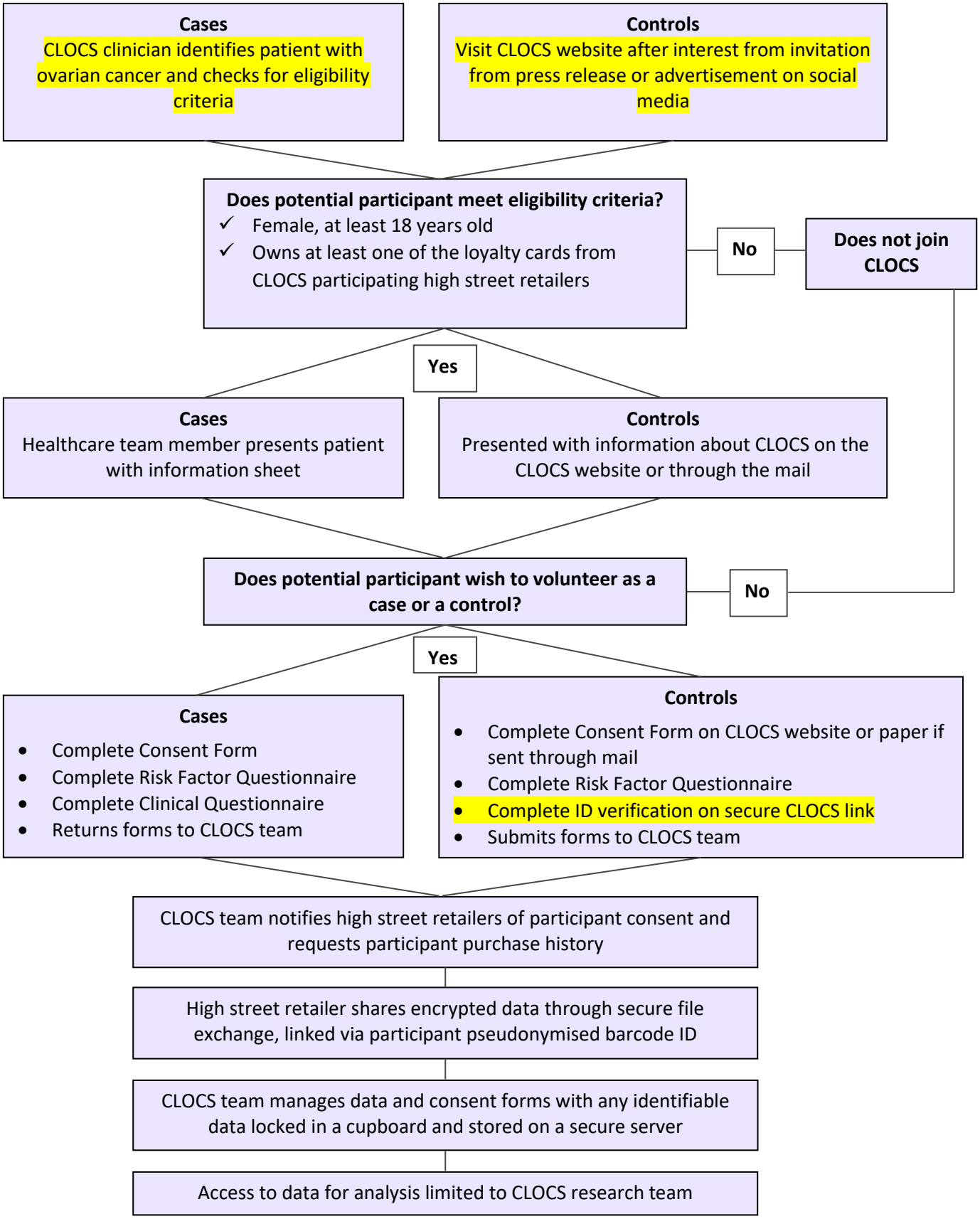
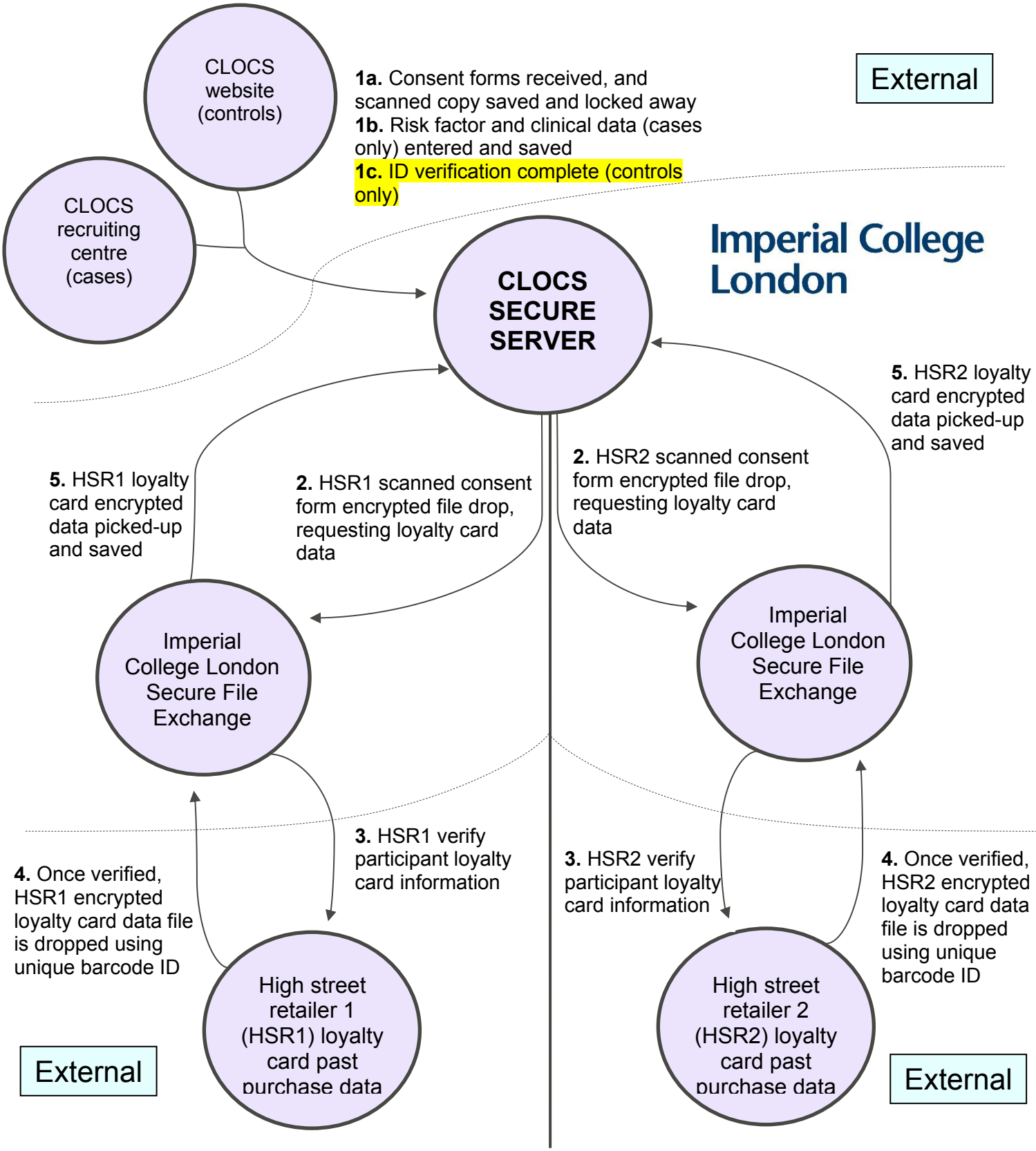
Appendix 1. Summary of CLOCS recruitment process



Appendix 2. Summary of CLOCS data flow



Appendix 3. Overview of research sites

Research Site	Investigator Name
Imperial College London, Department of Surgery and Cancer (Main Study Centre)	James Flanagan
Imperial College Healthcare Trust, St. Marys Hospital	Jon Krell
Brighton and Sussex University Hospitals University Trust	Rebecca Herbertson
NHS Greater Glasgow and Clyde, Gartnavel Royal Hospital	Ros Glasspool
Sandwell and West Birmingham Hospitals NHS Trust, City Hospital	Sudha Sundar
University College London Hospitals NHS Foundation Trust	Michelle Lockley
County Durham And Darlington NHS Foundation Trust, Darlington Memorial Hospital	Partha Sengupta
Walsall Healthcare NHS Trust, Manor Hospital	Lisa Richardson
Surrey and Sussex Healthcare NHS Trust, East Surrey Hospital	Samantha Weller
Airedale NHS Foundation Trust, Airedale General Hospital	Dan Lee
Swansea Bay University Health Board	Rachel Jones
Gateshead Health NHS Foundation Trust, Queen Elizabeth Hospital	Raj Naik
Leeds Teaching Hospitals NHS Trust, St. James University Hospital	David Jackson
NHS Lothian, Waverly Gate	Charlie Gourley
East Lancashire Hospitals NHS Trust, Royal Blackburn Hospital	Doina Badea
University Hospitals Bristol NHS Foundation Trust	Axel Walther
Royal Surrey County Hospital NHS Foundation Trust	Agnieszka Michael
The Royal Marsden NHS Foundation Trust	Susana Banerjee
Velindre NHS Trust	Emma Hudson
Cardiff & Vale University LHB, University Hospital of Wales	Aarti Sharma
South Tees Hospitals NHS Foundation Trust, James Cook University Hospital, Middlesbrough	Talal Mansy
West Hertfordshire Hospitals NHS Trust, West Hertfordshire Cancer Centre	S Radhika Vikram
Manchester University NHS Foundation Trust	Richard Edmondson