The YODA Project
Research Proposal Review

The following page contains the final YODA Project review approving this proposal.

The Yale University Open Data Access (YODA) Project
Yale University Center for Outcomes Research and Evaluation (CORE)
1 Church Street, Suite 200, New Haven, CT 06510

The YODA Project
Research Proposal Review - Final
(Protocol #: 2016-0884)

Reviewers:

- ☒ Nihar Desai
- ☐ Cary Gross
- ☒ Harlan Krumholz
- ☐ Richard Lehman
- ☒ Joseph Ross

Review Questions:	**Decision:**
1. Is the scientific purpose of the research proposal clearly described?	Yes
2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health?	Yes
3. Can the proposed research be reasonably addressed using the requested data?	Yes, or it's highly likely
4. Recommendation for this data request:	Approve

Comments:

No additional comments.

The YODA Project
Research Proposal Review

Revisions were requested during review of this proposal.
The following pages contain the original YODA Project review and the original submitted proposal.

The Yale University Open Data Access (YODA) Project
Yale University Center for Outcomes Research and Evaluation (CORE)
1 Church Street, Suite 200, New Haven, CT 06510

The YODA Project
Research Proposal Review - Revisions Requested
(Protocol #: 2016-0884)

Reviewers:

- ☒ Nihar Desai
- ☐ Cary Gross
- ☒ Harlan Krumholz
- ☐ Richard Lehman
- ☒ Joseph Ross

Review Questions:	**Decision:**
1. Is the scientific purpose of the research proposal clearly described?	No
2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health?	Yes
3. Can the proposed research be reasonably addressed using the requested data?	Unsure, further clarification from requestor is needed
4. Recommendation for this data request:	Not Approve

Comments:

We appreciate the data requestor's efforts to revise the submission in response to comments from the YODA Project. Unfortunately, as written, the proposal still does not offer sufficient clarity of purpose and methods. Our best guess is that this proposal has been written by a non-native English language speaker. We would strongly suggest collaborating with a native English language speaker in order to improve the clarity of the writing. The requestor also notes plans to disseminate these findings via the Cochrane Library of Systematic Reviews - does this imply that the review is being done under the umbrella of the Cochrane Collaborative? Investigators associated with the organization might assist in improving the clarity of the writing. Furthermore, all Cochrane reviews require registration in PROSPERO - much of the information required by PROSPERO is required by the YODA Project. Sending a link to that registration page might also improve clarity.

In terms of the substance needed for revision, please address the following 7 specific points:

1. Please clarify the "Brief Project Background and Statement of Project Significance". This section should focus only on the project background and be longer than 2 sentences in length. 2 paragraphs should provide sufficient background for the YODA Project reviewers to understand the scientific context for the work. And please explicitly describe the scientific value, or significance, of the work. Also, please use this section ONLY to discuss background and significance. As currently written, many aspects of the methods are described within this section of the proposal as well. In fact, the text remains redundant in multiple places.

2. As another example, the "Specific Aims of the Project" repeat several sentences of text related to the methods, this is not appropriate. Please explicitly note the scientific aims of the project. Please read the Specific Aims included in approved data requests, listed here under the Research Proposal column: http://yoda.yale.edu/table-3-data-requests-approved, and revise yours to improve clarity. This section should not include variables.

3. Each and every possible “purpose of analysis” has been checked off. Is this true? Please clarify the purpose- this

Principal Investigator

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2016-0884

General Information

Key Personnel (in addition to PI): **First Name:** jose miguel
Last name: fernandez
Degree: PhD, MPH, MBA, MSc
Primary Affiliation: Universidad Pompeu Fabra, Barcelona.

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

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Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

Associated Trial(s): NCT00653952 - A Phase 3, Randomized, Open-Label, Comparative Study of CAELYX® versus Paclitaxel HCl in Patients with Epithelial Ovarian Carcinoma Following Failure of First-Line, Platinum-Based Chemotherapy
A Phase 3, Randomized, Open-Label, Comparative Study of DOXIL/CAELYX® versus Topotecan HCl in Patients with Epithelial Ovarian Carcinoma Following Failure of First-Line, Platinum-Based Chemotherapy
What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

A Meta-analysis of current treatments ' efficacy for Relapsed Ovarian Cancer

Narrative Summary:
A systematic review and meta-analysis of relevant and similar Randomized Controlled Trials (RCTs) will enable greater precision in making an unbiased estimation of the effects of treatments (Overall Survival, Progression Free Survival, Treatment Adverse Effects, Overall Response Rate)
Inclusion criteria: Women with diagnosed Relapsed Ovarian Cancer (1 previous treatment at least)
RCTs will be searched using EMBASE, OVID, Cochrane Library of trials and other engines.
Following interventions will be included:
Paclitaxel (+/- Carboplatin)
Gemcitabine (+/- Carboplatin)
Topotecan
Pegylated Liposomal Doxorubicin (+/- Carboplatin, +/- Trabectedin)
Bevacizumab (+/- Gemcitabine/Carboplatin)

Scientific Abstract:
Background:
Ovarian cancer is the leading cause of gynecologic cancer mortality, responsible for an estimated 266000 new cases in 2013. Most patients will initially respond well to treatment, but unfortunately, approximately three quarters of all women treated will develop recurrent disease and will no longer be considered curable. Treatment after recurrence focuses on prolonging life and improving quality of life (Qol), but it heavily depends on the time since first relapse.
Objective:
To compare different treatment strategies (with or without platinum) for the relapsed, advance setting; including the newly added olaparib and bevacizumab, by using meta-analysis techniques (mixed treatment comparisons)
Study Design:
Meta-analysis of RCTs, Phase III trials, for Relapsed Ovarian Cancer Treatment, since 1994 up to now; to compare survival endpoints using the Cochrane Library Methodology. Comparative, non-interventional.
Participants:
Women with Relapsed Ovarian Cancer, in any condition and age, with at least one previous relapse to chemotherapy.
Main Outcomes and statistical Plan
Hazard Ratios and Odd Ratios of Overall Survival, Progression Free Survival, Time to Next Therapy, Treatment Related Serious Adverse Effects, Next Therapy choice. Also, a multivariate regression analysis using Individual Patient Level data; to stratify PFS and OS by
ECOG
Age
PFI (Platinum Free Interval) lenght
Treatment Choice (discrete variable)
Previous Cytoreductive Surgery (Secondary)
Time to First Subsequent Therapy
Third Line treatment

Brief Project Background and Statement of Project Significance:
The type and intensity of chemotherapy used routinely for women with advanced ovarian cancer has varied because of uncertainty
about the effectiveness of the different regimens. The objective of this review was to compare single drugs versus combinations of drugs,
platinum versus non-platinum, and newer (maintenance or targeted therapies) in women with advanced ovarian cancer.
Defining ECOG PS as Eastern Cooperative Oncology Group Performance Scale (0=asymptomatic patient, self dependent, to 4=patient totally handycapped and bed dependant); PFI as Platinum Free Interval, which depicts the time of Clinical Progression since the last Platinum-based chemotherapy administration (measured in months, usually); we will:

Make an adjusted Hazard Ratio (HR) comparison for OS and PFS, ORR for the dichotomous variables -across the follow up time or 60 months, the longer of both-
Bias control: Stratification and covariant adjustment (i.e. number of previous therapies), also adjusting for potential cross-overs. Fixed and Random effects when apply. We will use Kaplan-Meier curves with adjustments to continuous variables when needed, and by covariates. Obviously Fisher tests would be needed for proportions.
Handling of missing data: Censoring or adjudication.
PSA (Probabilistic Sensitivity Analysis) and OWSA (One Way Sensisitivy Analysis) will be performed once pooled, by ECOG PS, number of previous therapies, Ascites existence (y/n), age, and geographical spread, amongst other variables (i.e. PFI).
This is a confirmatory and exploratory (depending on the effect size variable) analysis.
To our knowledge, this will be the first study to analyze the true effects on Survival and Progression Endpoints in terms of covariates -not just the treatments-, either clinical baseline status, age, previous conditions, race, levels of CA-125 (Cancer Antigen 12), and other (if feasible) OMICS measurements; this will allow to predict the future success odds of incoming treatment strategies -to better fit to specific set of patients-.

Specific Aims of the Project:
Will be Hazard Ratios (HR) comparison for effect sizes of Overall Survival (OS) and Progression Free Survival (PFS).
Other outpluts are based on Overall Risk Ratio (ORR) (i.e. for the dichotomous variables).
Bias control: Stratification and covariant adjustment (i.e. number of previous therapies), also adjusting for potential cross-overs. Fixed and Random effects when apply. We will use Kaplan-Meier curves with adjustments to continuous variables when needed, and by covariates. Obviously Fisher tests would be needed for proportions.
To account for prediction of success in terms of covariates for treatment of Relapsed, Epithelial, Ovarian Cancer, by using a multivariate analysis controlling for as much variables as possible, using Individual Patient Data sourced from Yoda and other sites (including companies).

What is the purpose of the analysis being proposed? Please select all that apply. New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations
New research question to examine treatment safety
Research that confirms or validates previously conducted research on treatment effectiveness
Research that confirms or validates previously conducted research on treatment safety
Preliminary research to be used as part of a grant proposal
Summary-level data meta-analysis
Summary-level data meta-analysis will pool data from YODA Project with other additional data sources
Participant-level data meta-analysis
Participant-level data meta-analysis will pool data from YODA Project with other additional data sources

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
RCTs will be extracted from MEDLINE, Scopus, EMBASE, Cochrane Register of Trials, and Cancer Research registers of trials. We will also search for the proceedings of meetings and drug companies.
Our aim to source as much as we canPatient Level Data, to allow for a truly effective Multivariate Analyses, when needed.
Inclusion Criteria: Women with Relapsed (confirmed diagnosis) Ovarian, Epithelian Cancer, with/out previous cytoreduction (primary and/or secondary) surgery.
Exclusion Criteria: None
Selection criteria
Randomised trials of:
(1) single non-platinum versus non-platinum combination chemotherapy
(2) single non-platinum versus platinum combination chemotherapy
(3) non-platinum regimen versus the same regimen plus cisplatin
(4) single platinum versus platinum combination chemotherapy
(5) maintenance based therapies (triplets) versus traditional schema (the above 1-4 named strata)

The number of expected RCTs would be around 14-18, depending on the assessed quality.

Main Outcome Measure and how it will be categorized/defined for your study:
Hazard Ratios (Credible Interval, assigned by Fixed and/or Random effects models weight) of OS, PFS, TFST (Time to First Subsequent Treatment)
Odds Ratio of Overall Response Rate and Treatment Related Serious Adverse Effects (measured along all follow-up times, or at least, within 60 months of observations).
Fixed effects model approach shall be used preferably, but it will depend on the found variability across trials (tested by Cochrane Q-Test and I2).

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
Age, PS ECOG status, PFI Lenght, previous surgeries (primary and/or secondary), previous taxane based treatments. Ascites presence.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
none.

Statistical Analysis Plan:
Will be HR comparison for OS and PFS, ORR for the dichotomous variables.
Bias control: Stratification and covariant adjustment (i.e. number of previous therapies), also adjusting for potential cross-overs. Fixed and Random effects when apply. We will use Kaplan-Meier curves with adjustments to continuous variables when needed, and by covariates. Obviously Fisher tests would be needed for proportions.
Handling of missing data: Censoring or adjudication.
PSA and OWSA will be performed once pooled, by ECOG performance, number of previous therapies, ASCT existence (y/n), renal impairment, age, sex and geographical spread, amongst other variables.
This is a confirmatory and exploratory (depending on the effect size variable) analysis.
Kaplan Meier modelling will be using as much as possible.

Project Timeline:
Starting Date: ASAP
Publication Date: December 2016

Dissemination Plan:
ISPOR abstract: June 2016 (submission of previous findings)
Cochrane Library of Systematic Reviews: December 2016
The NEJM, 2017, full papers submission with key data and supplementary appendixes.

The YODA Project
Research Proposal Review - Revisions Requested
(Protocol #: 2016-0884)

Reviewers:

- ☒ Nihar Desai
- ☐ Cary Gross
- ☒ Harlan Krumholz
- ☐ Richard Lehman
- ☒ Joseph Ross

Review Questions:	**Decision:**
1. Is the scientific purpose of the research proposal clearly described?	No
2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health?	Yes
3. Can the proposed research be reasonably addressed using the requested data?	Unsure, further clarification from requestor is needed
4. Recommendation for this data request:	Not Approve

Comments:

This is an interesting proposal to meta-analyze RCT data examining interventions used to treat recurrent ovarian cancer. Unfortunately, further information is needed, preventing sufficient understanding of the investigators' approach and methods. Multiple sections of the proposal appeared to be copied and pasted, leading to redundant text without clarifying specifically:

1. The project background and significance

2. The specific aims of the project

3. The data sources to be used along with the inclusion/exclusion criteria (including: the investigators request only 2 trials - what additional trials will be available for this meta-analysis? how will this data be obtained? if the other trials will be limited to published reports, why is IPD for the 2 requested trials needed? would CSRs be sufficient for purposes of this work?)

4. The dichotomous main outcome measures (specifically, at what time period will these be ascertained and will this information be available for all trials, just the requested trials, and so forth); statistical analysis (specifically, will you use fixed or random effects?)

5. A clear narrative summary for the general public (this narrative summary includes information on inclusion criteria as currently written - but how will RCTs of these interventions be searched for and identified?).

6. Also, please provide definitions for PS ECOG status, PFI Length and please avoid abbreviations as much as is possible (or at least define them with first use).

Principal Investigator

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Last Name: fernandez
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Address: Corazon de Maria 3

City: Colmenar Viejo
State or Province: Madrid
Zip or Postal Code: 28770
Country: España

2016-0884

General Information

Key Personnel (in addition to PI): **First Name:** jose miguel
Last name: fernandez
Degree: PhD, MPH, MBA, MSc
Primary Affiliation: Universidad Pompeu Fabra, Barcelona.

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

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Certification

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Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

Associated Trial(s): NCT00653952 - A Phase 3, Randomized, Open-Label, Comparative Study of CAELYX® versus Paclitaxel HCl in Patients with Epithelial Ovarian Carcinoma Following Failure of First-Line, Platinum-Based Chemotherapy
A Phase 3, Randomized, Open-Label, Comparative Study of DOXIL/CAELYX® versus Topotecan HCl in Patients with Epithelial Ovarian Carcinoma Following Failure of First-Line, Platinum-Based Chemotherapy
What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

A Meta-analysis of current treatments ' efficacy for Relapsed Ovarian Cancer

Narrative Summary:
A systematic review and meta-analysis of relevant and similar trials will therefore analyse overall survival (OS), while analysis of combined data from similar RCTs will also enable greater precision in making an unbiased estimation of the effects of treatment.
Patients of any age, gender or ethnic origin and with diagnosed Relapsed Ovarian Cancer (whatever histology).
RCTs that investigate the following interventions will be included:
Paclitaxel (+/- Carboplatin)
Gemcitabine (+/- Carboplatin)
Topotecan
Pegylated Liposomal Doxorubicin (+/- Carboplatin, +/- Trabectedin)
Bevacizumab (+/- Gemcitabine/Carboplatin)
We will assess the effects of therapies on Survival and Quality of Life.

Scientific Abstract:
Background:
Ovarian cancer is the leading cause of gynecologic cancer mortality, responsible for an estimated 266000 new cases in 2013. Most patients will initially respond well to treatment, but unfortunately, approximately three quarters of all women treated will develop recurrent disease and will no longer be considered curable. Treatment after recurrence focuses on prolonging life and improving quality of life (Qol), but it heavily depends on the PFI since first relapse.
Objective:
To compare different treatment strategies (with or without platinum) for this setting; including the newly added Olaparib and Bevacizumab, as maintenance therapies -the first for an specific , BRCA-mutated, set of patients-, in terms of meta-analysis of survival and Quality of Life.
Study Design:
Meta-analysis of RCT, Phase III trials, for Relapsed Ovarian Cancer Treatment, since 1994 up to now; to compare survival and QoL endpoints using the Cochrane Library Methodology.
Participants:
Women with Relapsed Ovarian Cancer, in any condition and age, with at least one previous relapse to chemotherapy.
Main Outcomes and statistical Plan
Hazard Ratios and Odd Ratios of Overall Survival, Progression Free Survival, Time to Next Therapy, Treatment Related Serious Adverse Effects, Next Therapy choice. Also, a multivariate regression analysis using Individual Patient Level data; to stratify PFS and OS by
ECOG
Age
PFI (Platinum Free Interval) lenght
Treatment Choice (discrete variable)
Previous Cytoreductive Surgery (Secondary)
Time to First Subsequent Therapy
Third Line treatment

Brief Project Background and Statement of Project Significance:
Will be HR comparison for OS and PFS, ORR for the dichotomous variables.
Bias control: Stratification and covariant adjustment (i.e. number of previous therapies), also adjusting for potential cross-overs. Fixed and Random effects when apply. We will use Kaplan-Meier curves with adjustments to continuous variables when needed, and by covariates. Obviously Fisher tests would be needed for proportions.
Handling of missing data: Censoring or adjudication.
PSA and OWSA will be performed once pooled, by ECOG performance, number of previous therapies, ASCT existence (y/n), age, sex and geographical spread, amongst other variables (i.e. PFI, defined as Platinum Free Interval, in months)
This is a confirmatory and exploratory (depending on the effect size variable) analysis.
To our knowledge, this will be the first study to analyze the true effects on Survival and Progression Endpoints in

terms of covariates -not just the treatments-, either clinical baseline status, age, previous conditions, race, levels of CA-125 and other (if feasible) OMICS measurements; this will allow to predict the future success odds of incoming treatment strategies -to better fit to specific set of patients-.

Specific Aims of the Project:
Will be HR comparison for OS and PFS, ORR for the dichotomous variables.
Bias control: Stratification and covariant adjustment (i.e. number of previous therapies), also adjusting for potential cross-overs. Fixed and Random effects when apply. We will use Kaplan-Meier curves with adjustments to continuous variables when needed, and by covariates. Obviously Fisher tests would be needed for proportions.
To account for prediction of success in terms of covariates for treatment of Relapsed, Epithelial, Ovarian Cancer, by using a multirregression analysis.

What is the purpose of the analysis being proposed? Please select all that apply. New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations
New research question to examine treatment safety
Research that confirms or validates previously conducted research on treatment effectiveness
Research that confirms or validates previously conducted research on treatment safety
Summary-level data meta-analysis
Summary-level data meta-analysis will pool data from YODA Project with other additional data sources

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
Data published and Patient Level Data.
Inclusion Criteria: Women with Relapsed (confirmed diagnosis) Ovarian, Epithelian Cancer, with/out previous cytoreduction (primary and/or secondary) surgery.
Exclusion Criteria: None

Main Outcome Measure and how it will be categorized/defined for your study:
Hazard Ratios (Credible Interval, assigned by Fixed and/or Random effects models weight) of OS, PFS, TFST (Time to First Subsequent Treatment)
Odds Ratio of Overall Response Rate and Treatment Related Serious Adverse Effects

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
Age, PS ECOG status, PFI Lenght, previous surgeries (primary and/or secondary), previous taxane based treatments. Ascites presence.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
none.

Statistical Analysis Plan:
Will be HR comparison for OS and PFS, ORR for the dichotomous variables.
Bias control: Stratification and covariant adjustment (i.e. number of previous therapies), also adjusting for potential cross-overs. Fixed and Random effects when apply. We will use Kaplan-Meier curves with adjustments to continuous variables when needed, and by covariates. Obviously Fisher tests would be needed for proportions.
Handling of missing data: Censoring or adjudication.
PSA and OWSA will be performed once pooled, by ECOG performance, number of previous therapies, ASCT existence (y/n), renal impairment, age, sex and geographical spread, amongst other variables.
This is a confirmatory and exploratory (depending on the effect size variable) analysis.
Kaplan Meier modelling will be using as much as possible.

Project Timeline:
Starting Date: ASAP
Publication Date: December 2016

Dissemination Plan:

ISPOR abstract: June 2016 (submission of previous findings)
Cochrane Library of Systematic Reviews: December 2016
The NEJM, 2017, full papers submission with key data and supplementary appendixes.