Protocol for the Outcomes Study

A study in the RESPOND Consortium

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1. PROTOCOL SUMMARY

Full title: The RESPOND Outcomes Study

Short title: Outcomes

Summary:
The RESPOND Outcomes study is a research study around use of antiretroviral and other relevant drugs and long-term clinical outcomes in patients living with HIV. Data collected in this study will be used to answer key unanswered questions regarding treatment of people living with HIV.

The specific objectives, falling into three main categories, are as follows:

1. Monitor the uptake of newer antiretroviral treatment (ART) drugs and drugs for treatment of co-infections and co-morbidities;
2. To evaluate the safety profiles of the newer individual ART drugs when used in routine clinical practice as part of either first-line or subsequent treatment regimens.
3. Investigate long term outcomes and clinical disease progression overall and in specific sub-groups

The Outcomes study is a collaboration between investigators from clinics and cohorts across Europe, Australia and Southern America with a willingness to share data and to use a common follow-up schedule and assessment. Participating sites have a commitment to continue to follow this large cohort that is heterogeneous in both its demographic profile and in ART prescribing patterns thus resulting in enough power to answer many key clinical questions.

The Outcomes study is a study in the RESPOND International Cohort Consortium of Infectious Diseases. RESPOND is an innovative, flexible and dynamic cohort consortium for the study of infectious diseases, including HIV, built as a generic structure for facilitating multi stakeholder involvement. In RESPOND all collected data is part of a common data repository or 'data lake', which is stored in a database located at CHIP, Rigshospitalet, Copenhagen, Denmark. Data collection in RESPOND is modular with a core data collection module onto which additional modules/studies can be added. Pseudonymised patient data can be entered manually via an online secure platform or be electronically transferred from existing local, regional or national data structures to the data lake.

In the Outcomes study data will be collected at enrolment and at annual follow-up (FU) visits. For patients living with HIV-1 enrolled and under FU, demographic, laboratory, therapeutic and clinical data on HIV and viral hepatitis will be collected once a year. Clinical event data (except AIDS other than AIDS defining malignancies) will be collected in real-time on RESPOND event forms.

Study start date (date open for recruitment or date of first participant enrolled)

2. STUDY PURPOSE

2.1 BACKGROUND AND RATIONALE

The cessation of earlier large pharmacovigilance studies in patients living with HIV, such as the D:A:D study, has left a gap in knowledge for all people living with HIV and their healthcare providers. The treatment of HIV and related co-infections and co-morbidities is not static. New drugs continue to be licensed and although early data suggest that the toxicity profile of these drugs is favourable, it is important to monitor individuals for potential risks of clinical events over the long term and investigate whether there are substantial differences in the adverse effect profile in different population groups such as those defined by age, ethnicity, HIV risk group, CD4 count, viral hepatitis and other co-infections. The past decades have taught us that key questions will continue to arise which will require rigorous approaches to answer them and support the need for a systematic international surveillance.

The increased life expectancy of people living with HIV has resulted in an ageing population of people living with HIV [1, 2]. There is furthermore some concern that HIV may lead to premature ageing, with some comorbidities occurring at a younger age than expected [3]. Whether this simply reflects the younger age distribution of the people living with HIV and/or lifestyle and behavioural factors remain to be explored. As part of the normal ageing process, the clearance of various substances, includingrna), may be substantially decreased with increased risk of drug toxicity [4]. Treatment of age-related co-morbidities such as hypertension, diabetes and CVD, but also tuberculosis TB), which has a high prevalence in eastern European countries, may additionally result in poly-pharmacy and increase the potential for drug-drug interactions and arise concerns over new drug-related clinical risks that have, to date, not been noted.

Chronic hepatitis C virus (HCV) infection is the leading cause of end-stage liver disease and liver-related death among HIV infected individuals in the developed world [5]. Effective and well-tolerated direct acting antivirals (DAAs) against HCV have been available since 2013, and communitywide eradication of HCV appears possible [6]. Sustained virologic response (SVR) rates >95% have been reported in both HCV monoinfected persons and in those coinfected with HIV [7]. Although the risk of liver-related complications is reduced after SVR, complications can still occur after many years [8]. Which patients are at risk of liver-related complications after SVR, and to which extent HIV-related factors influence this risk has not been well-defined. Consequently, the optimal and most cost-effective way to monitor patients for liver-related complications after SVR remains unclear. Whether HCV therapy also has any significant impact on lowering the risk of extra-hepatic morbidity and mortality such as cardiovascular disease and non-hepatic malignancies remains uncertain. Large well-designed studies are required to study this.

The Outcomes study will prospectively collect data to address key unanswered questions regarding the short- and long-term clinical outcomes and safety of different ARVs and drugs for treatment of co-infections and co-morbidities. Due to the increased prevalence of several comorbidities and co-infections in people living with HIV, there are increasing demands for a personalised approach to treatment. The study specific Scientific Interest Group (SIG) directing the study has extensive experience in building and validating risk-score models for cardiovascular disease [9] and chronic kidney disease [10] in patients living with HIV. Risk score models will be used to identify the risks and benefits of specific therapies in terms of risk of specific events, such as cardiovascular disease or cancer, such that the most appropriate antiretroviral regimen can be directed towards those most likely to benefit. Risk score models can be built for liver disease, cancer, or specific cancers and the role of ARVs considered through the number needed to treat to benefit or harm.

The Outcomes study in RESPOND is a collaboration between investigators from clinics across Europe, Australia and Southern America with a willingness to share data across cohorts, to agree to a common follow-up schedule and assessment, and to continue to follow this large cohort that is heterogeneous in both its demographic profile and in ARV prescribing patterns, resulting in

enough power to answer many key clinical questions.

In RESPOND all collected data is part of a common data repository or 'data lake', which is stored in a database. However, the data collection itself is project-based or modular, with specific studies consisting of targeted data collection for subgroups of participants. A participant can be part of several specific studies. All sites/centres will collect data to one or more specific studies depending on their participant inclusion. The common data repository allows for important cross-cutting research across modules and studies, with important synergies, and costs savings in terms of data collection. For most participants in RESPOND core data is collected for the following categories: Demography and basic clinical information; Relevant virological and immunological information; Laboratory information regarding organ function and biomarkers for metabolic illness, Co-infections including genotype and relevant paraclinical information; and Antiretroviral Treatment (ART) information.

2.2 AIMS AND OBJECTIVES

1. Monitor the uptake of newer ARVs and drugs for treatment of co-infections and co-morbidities; to describe changes over time and country specific uptake and use of specific ARVs as well as in diverse demographic groups

2. Monitor immunologic and virologic responses among persons exposed to newer individual ARVs

3. Evaluate the short- and long-term safety profiles of the newer ARVs when used in routine clinical practice as part of either first-line or subsequent treatment regimens, and whether safety signals are reversible on discontinuation of the offending ARVs

4. Investigate if safety signals are increased in some patient sub-groups (e.g. those defined by age, gender, ethnicity, HIV-risk group, viral hepatitis- TB and other co-infections, ongoing viremia and across CD4 count strata) in order to build clinical risk prediction scores to aid effective strategies for risk reduction, as well as assessing the risk and benefit for the individual of any antiretroviral or group of antiretrovirals.

5. Investigate long term outcomes and clinical disease progression overall and in specific sub-groups (e.g. those defined by age, gender, ethnicity, HIV-risk group, viral hepatitis- TB and other co-infections, ongoing viremia and across CD4 count strata) and to develop predictive risk-scores for the development and outcomes to enable personalized decisions regarding risk and benefit of specific treatments in different demographic groups

3. METHODOLOGY

3.1 STUDY DESIGN
The Outcomes study is a prospective, non-interventional, non-randomized, open-label multi-cohort observational study. Standardised data collection based on local routine data collection will take place once a year. Clinical event data (except AIDS other than AIDS defining malignancies) will be collected in real-time.

3.2 ENROLMENT
Participating clinics will enrol eligible persons living with HIV. Some clinics will enrol all their eligible persons living with HIV, and others will enrol a random sample.

3.3 DATA ITEMS COLLECTED

The following data items are collected:

Demography and basic information: Date of birth, gender, country of origin, ethnicity, height, weight, date of first HIV-1 positive test and mode of HIV-1 transmission.

Laboratory data: Relevant routine virological and immunological data for characterization of the HIV infection, hepatitis C and other relevant co-infections, as well as routine laboratory data that describe the function of the bone marrow, kidneys and liver. Biomarkers of metabolic disease will also be collected.

Medical treatment: All HIV medicine, including start- and stop dates and reason for discontinuation. Medical treatment related to co-infections and co-morbidities.

Clinical events: AIDS, myocardial infarction, stroke, invasive cardiovascular procedures, kidney failure, liver failure, cancer, bone fractures, cause of death.

3.4 DATA COLLECTION

Study sites/clinics will collect data from participating patients at the time of enrolment, and once a year hereafter. At the time of enrolment, retrospective data are collected up to five years back if relevant and available. Patient record data capture for the Enrolment and FU forms is done by manual data keying or electronically. Manual data keying is performed in a secure online browser-based platform called REDCap. Electronic data capture entails local extraction of data from clinical electronic databases and submission using the RESPOND electronic submission tool (REST) to the RESPOND common data repository. Data is submitted in the HIV Cohorts Data Exchange Protocol (HICDEP) format.

Data on specific clinical events (cancer, stroke, myocardial infarction, invasive cardiac procedure, malignancies, renal failure, liver failure, bone fracture and cause of death) will be captured in real-time via specific event forms manually keyed into REDCap.

4. DATA ANALYSIS METHODS

4.1 POWER CONSIDERATIONS FOR CLINICALLY RELEVANT ENDPOINTS

Endpoints

AIDS events and serious non-AIDS events (including cardiovascular disease, metabolic dysfunction, liver-, renal disease, malignancies) and mortality.

Large safety studies are required to reliably address associations with less frequent clinical events such as renal, cardiovascular disease or cancer. Many post-marketing safety studies are at high risk of type-II errors due to limited size and often relatively homogenous study population with few or no co-morbidities. We propose to include 30,000 persons over the period of the study; we estimate that around half of these will be receive INSTI based therapy. We would anticipate that 10,000 persons will be included at the start of the study (1/10/2017) and including 10,000 more persons each year in the following two years. These patients will be included from existing cohorts, and by extending participation and inclusion of patients living with HIV from across sites in RESPOND.

Table 1: Anticipated event rates

Event	Rate / 1000 PYFU	Source
Chronic kidney disease	8.6	D:A:D, Mocroft, personal communication

Cardiovascular disease (CVD)	5.4	[9]
Cancer	7.6	[11]
Death	12.7	[2]
AIDS	15.0	EuroSIDA, Mocroft, personal communication

Based on the event rates above, and assuming 10,000 new persons are recruited evenly over the year, and 10% LTFU per year, we anticipate clinical event rates to accrue as shown in the Table below.

Table 2: Clinical event rates and anticipated detectable differences between persons receiving integrase inhibitors vs. other antiretroviral drugs

				Clinical events				
Year	**N under FU at start**	**N under FU at end**	**PYFU in year**	**Chronic kidney disease**	**CVD**	**Cancer**	**AIDS**	**Death**
2017	10000	17671	13991	120	76	106	210	178
2018	18521	25224	22058	190	119	168	331	280
2019	26074	31919	29209	251	158	222	438	371
2020	32769	37853	35548	306	192	270	533	451
			Total	**867**	**544**	**766**	**1512**	**1280**
Detectable difference				**22%**	**30%**	**24%**	**18%**	**17%**

Assuming 10% LTFU per year and no additional follow-up after the end of 2020, the detectable differences with 80% power are shown in Table 2. For example, we will have 80% power to detect a difference of 22% or greater in chronic kidney disease (CKD) when comparing those exposed to INSTI with those who are unexposed to INSTI with a 5% type I error, assuming an average incidence of CKD of 8.6/1000 PYFU.

4.2. GENERAL CONSIDERATIONS - ANALYSIS

Our objectives fall into two broad categories:

1) Uptake and use of ART and other treatments and immunologic and virologic outcomes

2) Associations between short- and long-term exposure to ART or drugs for treatment of co-infections and risk of AIDS and non-AIDS clinical outcomes

Regarding category 1:

Descriptive rates of starting therapy will be calculated overall and for specific sub-groups defined by age, gender, ethnicity, HIV risk and by current CD4 cell count and current HIV viral load. Rates will further be compared between different European regions (East, West, North, South) and Australia. Confounding by indication and the non-random selection of participants into RESPOND will be considered in interpretation of this data.

Basic descriptive statistics will be used to describe clinical characteristics at time of starting therapy. Poisson regression will be used to determine the factors associated with starting or discontinuing therapy during prospective follow up from 2012 to the end of follow-up stratified by geographical regions. Factors to be considered include age, age at infection, calendar year, gender, ethnicity, HIV transmission group, prior AIDS defining event, HBV/HCV co-infection, prior diagnosis of diabetes, hypertension, cardiovascular disease (CVD), end-stage liver disease (ESLD), cancer, chronic kidney disease (CKD), fractures and current treatment (non vs ART),

current regimen (PI/NNRTI/NRTI), history of antiretrovirals, and CD4 cell count and HIV viral load.

Regarding category 2: Objectives in this category principally involve using univariable and multivariable Poisson regression models to identify factors associated with AIDS and non-AIDS clinical events. Factors to be considered include use of specific antiretrovirals as well as age, gender, HIV transmission group, ethnicity, prior AIDS, hepatitis B/C status, CD4 cell count, HIV-RNA and factors a priori known to be associated with risk of the outcome.

4.3 POSSIBLE LIMITATIONS

As for observational studies in general, possible limitations of the Outcomes study include unmeasured confounding and confounding by indication. Variables may be missing from some participants or cohorts which may introduce bias and loss of statistical power. A wide range of sensitivity analyses will assess the robustness of findings taking into consideration the quality of data from individuals or from cohorts.

5. STUDY SUBJECTS

5.1 INCLUSION CRITERIA

1. Signed Informed consent for the Outcomes study, if required by local/national legislation
2. Signed informed consent for the RESPOND consortium and data repository, if required by local/national legislation
3. Age ≥ 18 years of age
4. Confirmed HIV-1 infection
5. Persons receiving integrase inhibitor (INSTI) based antiretroviral therapy if have started after the later of 1/1/2012 and local cohort enrolment (i.e., during prospective follow-up in the cohort and after 1/1/2012) and have a CD4 and HIV viral load in the 12 months prior to starting INSTI or within 3 months after starting INSTI.
6. ART experienced and ART naïve persons not receiving INSTI if have a CD4 and HIV viral load in the 12 months prior to baseline or within 3 months after baseline (here, the latest of 1/1/2012 or cohort enrolment).
7. Persons lost to follow-up or who died before RESPOND enrolment should therefore still be included in the Outcomes study, provided they satisfy the other inclusion criteria.

5.2 EXCLUSION CRITERIA

1. Persons receiving INSTI before 1/1/2012 are excluded from the Outcome study
2. Persons aged < 18 at baseline are excluded from the Outcome study

6. RISK & BENEFITS FOR PARTICIPANTS

6.1 RISKS

Participation in the Outcomes study does not include any risk for the participants. The study does not test any drugs and participation in this study does not interfere with the treatment/care participants may receive at the clinic. Patients do not need to receive ART in order to participate in the study. Pregnant women may participate in the study, as no interference with their treatment or pregnancy in any way will take place.

6.2 BENEFITS

There are no direct benefits to the participants. However, the benefit of conducting observational research includes advancing scientific understanding of HIV infection and other co-infections and co-morbidities and their complications; this knowledge guides international and European treatment recommendations to the benefit of people living with HIV.

7. BIOGICAL MATERIALS

No biological materials, only observational patient record data is collected in the Outcomes study.

8. INFORMATION FROM PATIENT RECORDS

8.1 PATIENT RECORD DATA

Staff at the clinics in the Outcomes study will extract data from the patient records of enrolled participants, de-identify and submit to the Coordinating Center in the required CRFs.

8.2 DATA BASE

Data collected in this study will be submitted to and stored in the RESPOND common data repository or 'data lake' (see Appendix 1 on RESPOND).

9. PERSONAL DATA HANDLING AND APPROVALS

9.1 CONFIDENTIALITY OF STUDY PARTICIPANTS

The confidentiality of all study participants will be protected in accordance with Good Clinical Practice (GCP) Guidelines and national regulations.

Study participants are de-identified and pseudonymised with a Unique Patient Identifier (PID). A de-coding list is held in a safe location by the individual site and it is the responsibility of cohort PI/local study staff to secure this. All data shared contain the PID number and no unique person identifiers. Study data is stored in the RESPOND data repository at the Coordinating Center and protected in accordance with current regulatory laws and approved by The Danish Data Protection Agency (DK: Datatilsynet, approval no. 2012-58-0004, RH-2018-15, I-Suite nr.: 6140).

Every reasonable step will be taken to protect the privacy of participants' health information and to prevent misuse of this information. The participants' records (paper/digital) may be seen by Institutional Review Boards (IRBs) or Ethic Committees (ECs) who review the study to make sure it is ethically acceptable and by research staff and study monitors, and their designees.

Participants will in the Informed Consent forms and Data Protection information sheet be informed about the above conditions.

9.2 REGULATORY APPROVAL

It is the responsibility of each participating site/cohort to ensure that all necessary documents and approvals by the site's Ethics Committee (IRB or IEC) are obtained according to local/national regulations prior to initiating study related activities and in case of any future amendments to the study protocol.

CHIP is the data protection officer (DPO) for the Outcomes study data and is following General Data protection Regulation (GDPR) in Europe.

10. ECONOMY AND STUDY ADMINISTRATION

10.1 STUDY SPONSOR

This in an investigator-initiated study. The study has been initiated by the Outcomes Scientific

Interest Group (SIG) in the RESPOND consortium.

Sponsor and study coordinator is CHIP, which is an independent research institution at the Department of Infectious Diseases at Rigshospitalet, Copenhagen, Denmark.

10.2 COLLABORATORS

The Outcomes SIG is the study group responsible for the scientific aspects of the Outcomes study. The scientific output is being overseen by the RESPOND Scientific Steering Committee, which is an independent body responsible for overseeing the different data modules, and approving initiation of new research projects. The SSC comprises 2 co-chairs, Study Coordination Center representatives, 1 representative from each cohort submitting data to RESPOND, the leads of active Scientific Interest Groups, community representatives, and external experts as agreed by the SSC. This includes researchers, statisticians, clinicians as well as representation from the HIV community.

For further information on RESPOND governance structure please consult the RESPOND Consortium description (Appendix 1).

10.3 FUNDERS

RESPOND and the Outcomes study has received funding from ViiV Healthcare LLC [2 million Euros] and Gilead Sciences [2 million Euros]. Additional support has been provided by participating cohorts contributing data in-kind and/or statistical support: Austrian HIV Cohort Study (AHIVCOS), The Australian HIV Observational Database (AHOD), CHU Saint-Pierre, University Hospital Cologne, The EuroSIDA cohort, Frankfurt HIV Cohort Study, Georgian National AIDS Health Information System (AIDS HIS), Modena HIV Cohort, San Raffaele Scientific Institute, Swiss HIV Cohort Study (SHCS), and the Royal Free HIV Cohort Study.

10.4 SITE REIMBURSEMENT

The participating sites/clinics/cohorts are reimbursed for completed deliverables, i.e. the relevant CRFs submitted in REDCap and/or REST.

11. REMUNERATION AND BENEFITS

11.1 NO REMUNERATION

No remuneration will be paid to the study participants. There are no direct benefits to the study participants. However, the benefit of conducting observational research includes advancing scientific understanding of HIV infection and other related co-infections and co-morbidities and their complications and risk factors for these conditions; this knowledge guides international and European treatment recommendations to the benefit of people living with HIV or at high risk of HIV

12. RECRUITMENT OF STUDY PARTICIPANTS AND INFORMED CONSENT

12.1 RECRUITMENT

Participating sites will ask eligible persons living with HIV to participate in the Outcomes study. Participation in a study in RESPOND also require participation in the RESPOND data repository

The local site Principal Investigator (PI) or his/her designee will inform the participant of all aspects pertaining to his/her participation in the Outcomes study and the RESPOND data repository.

12.2 INFORMED CONSENT PROCEDURE

Prior to study start the participant will be informed verbally by a doctor or study nurse about the study and will receive written information about the study and about data protection. If a participant wishes to have time to consider their decision this will be arranged with staff at site.

The participant will have the opportunity to ask questions.

The participant will be informed that participation is voluntary and that he/she can withdraw his/her consent at any time without any consequence for his/her treatment or future relationship to the clinic/hospital.

The Patient Informed Consent form for the Outcomes study and for RESPOND will be signed before any study related activities can begin (See Appendix 1 for RESPOND sample documents and sample Outcomes study Informed Consent form in Appendix 2).

13. PUBLICATION OF RESULTS

13.1 PUBLICATION AND AUTHORSHIP

The findings from this study, positive, negative or inconclusive, are intended to be published in peer-reviewed journals and/or presented at medical conferences ('Publication'). Publication will be in accordance with international recognized scientific and ethical standards concerning publications and authorships. Copyrights concerning Publication of the study remain with the authors of the Publication, regardless of any other provisions regarding intellectual property rights.

Authors provide the study coordinating center with a copy of manuscripts and/or abstracts at least thirty-five (35) business days in advance of any submission for publication and ten (10) business days in advance of any submission to a scientific meeting for approval by the RESPOND SSC (for details on RESPOND see Appendix 1). All publications and presentations will be listed on the CHIP webpage, www.chip.dk

14. ETHICAL CONSIDERATIONS

14.1 ETHICAL CONDUCT OF THE STUDY

The study will be conducted according to the Declaration of Helsinki in its current version. The requirements of Good Clinical Practice (GCP) as defined in current EU GCP Directive. Human Subject Protection and Data Protection Acts or with the local law and regulation, whichever affords greater protection of human subjects.

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