COHERE
Manual of Operations

Version 4.6

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Appendices provided in a separate document are:

Regional Coordinating Centres

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1. COHERE Introduction

1.1. Mission and scientific emphasis

COHERE (Collaboration of Observational HIV Epidemiological Research Europe) is a unique collaboration among 39 European cohorts of HIV-infected persons representing 31 European countries. The cohorts participating in COHERE are included because of their proven ability to raise scientific questions and collect good quality data on patients at clinical sites linked to that cohort. A list and a brief description of participating cohorts can be found in Appendices 1 and 2 respectively. The 2013 COHERE Merger included 299,690 participants.

COHERE's mission is to conduct hypothesis-driven epidemiological research on the prognosis and outcome of HIV-infected people from across Europe. The questions investigated are questions for which sufficient data elements are found in contributing cohorts and that require large sample sizes, long-term follow-up, or large representativeness (e.g. the incidence and determinants of emerging and/or rare events or their prognosis) and which the contributing cohorts cannot answer individually and which do not overlap with existing collaborations between participating COHERE cohorts. COHERE's size allows for comparisons across the age categories and provides a mechanism to rapidly compile datasets to address novel research.

To maintain consistency, it was essential to put in place a governance framework of procedures and management for developing projects and seeking funds described in this document. Each participating cohort has an operationally functioning structure for the collection of data that is governed and funded separately from COHERE. Each cohort's integrity largely depends on a high degree of continuing scientific autonomy and independence. Most cohorts participating in COHERE were established nearly 20 years ago and significant human and financial resources have been invested to develop their infrastructure and databases. Furthermore, cohorts' funding bodies have a strong sense of ownership over cohorts' infrastructure and data.

COHERE and the EuroCoord Network of Excellence have capitalized on and further developed this existing infrastructure while ensuring that certain procedures relevant to the conduct of COHERE are done in a harmonized way by all participating cohorts. The prerequisite for cohorts to participate in COHERE is active contribution – the COHERE Executive Committee will discuss with Cohorts that do not participate in two consecutive mergers (provided that they have the data) regarding their continued participation in COHERE.

Bridging funding from the French National Agency for Research on AIDS and Viral Hepatitis (ANRS), the Dutch HIV Monitoring Foundation and the Danish Augustinus foundation was received for the first years of COHERE's existence. Furthermore, grant funding for specific projects was obtained from the UK's Medical Research Council and a Swiss Bridge Award. COHERE is one of the four founding research collaborations of EuroCoord, a FP7 European Union-funded Network of Excellence. An overview of the COHERE-specific workpackages in EuroCoord can be found in Appendix 3.

It is important to stress that the participating cohorts in COHERE appreciate the opportunity that the EuroCoord collaboration provides to further expand and strengthen the collaborative efforts that have been ongoing within the European continent in the last decade and to collaborate with other regions of the world.

A main infrastructure concern is the risk of deterioration of the single participating cohorts because of lack of funding. The EU funding obtained through EuroCoord for the cohort coordination effort within COHERE will be minimal relative to individual cohort's annual budgets.

It is, therefore, imperative that each cohort maintain the support of their main sponsors. Additionally, many of the cohorts in COHERE are competing for funds from public funding agencies and the measurable outcome of their scientific work is publication in peer-reviewed journals. For COHERE to be successful, each of the cohorts must maintain their autonomy and scientific agendas aside from the COHERE research plan and freely publish on the research questions they are addressing or planning to address. However, it may be that certain analyses that individual cohorts are conducting would provide more robust answers if the entire COHERE database were used.

2. Scientific Collaboration Management and Governance Structure

2.1. COHERE Steering Committee

2.1.1. Principles

The COHERE Steering Committee (COHERE SC) is the governing body which oversees the operation of the COHERE collaboration in accordance with its principles:

1. COHERE should not threaten the scientific programme of individual participating cohorts nor should it compete with those of existing cohort collaborations
2. The scientific questions to be addressed in COHERE are based on a consensus on relevant scientific issues not already addressed in the individual cohorts and the collaborations. Each of these scientific questions therefore carries added value as compared to current scientific plans of contributing cohorts and collaborations.
3. The individual contributing cohorts must declare their interest to participate.
4. Individual cohorts may veto the use of their data in any new projects.

2.1.2. Composition

The COHERE SC, comprised of representatives from participating cohorts, is the governing body of the COHERE Collaboration. However, a certain level of executive power is transferred from the COHERE SC to the COHERE EC, the precise nature of which has been formulated and approved by the COHERE SC.

The COHERE SC is intentionally large in membership in order to serve the principle of inclusiveness in any decision-making process. The COHERE SC is comprised of the Chair, the Chair elect, one patient community representative, representatives of the participating cohorts and one representative of each of the two Regional Coordinating Centers (RCCs), Theme Leads and the leads of ongoing projects and, occasionally, external experts.

Each contributing cohort has one seat on the COHERE SC if their number of patients under active follow-up for the preceding year is less than 4,000 and two seats if this number is larger than 4,000. The Theme Leads and ongoing scientific project leads are invited to attend the Steering Committee meetings until the theme ceases to exist or project is completed. External experts or representatives from other collaborations may also be co-opted to the COHERE SC to maintain a

multidisciplinary approach in the collaboration. However, only representatives of participating cohorts hold voting rights; all others members are considered to be “silent members”. Current members of the COHERE SC and Executive Committee (COHERE EC) can be found in Appendix 4

2.1.3. Role of the COHERE SC

The COHERE SC meets face-to-face at least once annually, but preferably twice. Teleconferences may replace one of the annual face-to-face meetings. Teleconferences may also be organized as required.

The voting members of the COHERE SC (i.e. the cohort representatives, not silent members) elect the Chair. The voting SC representatives from the two regions elect their respective regional representatives; see details below in section 2.2.1. The COHERE SC sets the principles governing the management of the overall collaboration and the budget and approves the semi-annual progress report. COHERE election rules can be seen in Appendix 5.

The COHERE SC evaluates and approves scientific proposals and analysis plans (see below for process of approval of projects~~)~~. A project will be conducted within COHERE based on a consensus within the COHERE SC. However, if a cohort has not supported a project, this cohort may decide to opt out of contributing their data to a project prior to its implementation.

The COHERE SC monitors and assesses the progress of the work of the COHERE collaboration and oversees the results of all analyses performed with the data mergers. The COHERE SC also oversees the dissemination of these results, via publication in the scientific literature and presentation at conferences and workshops.

The COHERE SC approves the creation of Theme Groups to lead project groups within the Theme and ad-hoc project teams to develop specific scientific projects or logistical aspects. It also approves the rules governing quality control and the SOPs for collecting cohort data.

2.1.4. Decision Making Process of the COHERE SC

The COHERE SC in its decision-making will operate by consensus. Very occasionally during its business, voting by SC members (i.e. cohort representatives, not silent members) may be required. In such a situation the majority vote will determine the course of action. In the case of a split vote (less than a 10% difference between those for and against), the Chair seek to achieve a majority vote through negotiation and thereby consensus.

2.1.5 Inclusion of potential new cohorts on the COHERE SC

Cohorts wishing to join COHERE are required to complete the COHERE New Cohort Data Profile (Appendix 13) and submit it to the RCC Leads. The profile will then be reviewed by the RCCs and EC before being sent to the SC for endorsement. The decision on whether to include the potential cohort will be reached by consensus. The SC representatives will have two weeks to endorse or oppose the inclusion of the potential cohort. If a cohort opposes the inclusion, the SC representative must provide clear justification. Any questions raised by this justification must be forwarded to the PI of the potential cohort immediately by the respective RCC (the RCC the cohort will adhere to upon inclusion in COHERE) so the concerns can be addressed without delaying the inclusion process. Oppositions submitted without clear justification will not be considered.

The respective RCC lead will notify the potential cohort's PI of the COHERE SC's final decision once a consensus has been reached.

2.2. COHERE Executive Committee

2.2.1. Composition

The COHERE EC consists of:

1. The Chair and Chair Elect
   a. The Chair - elected by the Steering Committee to serve 5 years with the option of running for a second term
   b. The Chair Elect - elected by the Steering Committee to work alongside the Chair one year before the Chair steps down from office
   c. The Chair should announce their intention to run for a second term one and a half years before the end of their first term so that there is time to arrange an election.
2. Six cohort representatives: three from cohorts relating to each of the 2 RCCs nominated and elected by the cohorts within the region. Cohorts may nominate individuals that are not cohort leads if they wish to delegate EC membership. – Cohort representatives are elected for a five-year period with the option of standing for a second term, not all representatives are up for election simultaneously, of the six representatives elected the first time, two representatives selected by drawing lots will be up for re-election after two years, thereafter the five year term will apply for all.
3. Two RCC Leads, one from Bordeaux and one from Copenhagen (the leads need not be the Head of the RCC).
4. Two EuroCoord COHERE specific Scientific and Infrastructure work package leads.

COHERE election rules for EC can be found in Appendix 5.

Additional leads that are not full voting members of the Executive Committee may join Committee teleconferences and meetings for scientific agenda items and will be allowed to stay during the meeting/the teleconference as observers for other sessions if they so wish unless there is an item reserved for the voting members only.

1. Two representatives for the paediatric cohorts
2. Research theme leads for as long as theme exists (for current themes and theme leads, see Appendix 4).
3. Project leads who fall outside the themes, for example Late Presenters.

2.2.2. Role of the COHERE EC

The principal role of the COHERE EC is to oversee the day-to-day conduct of the collaboration on behalf of the COHERE SC, and hence the functions of the two Regional Coordinating Centres.

Hence, the COHERE EC is the formal link between the governing body, the COHERE SC, and COHERE operations.

The COHERE EC reviews scientific projects to ensure that they conform to the scientific principles of the collaboration, and assesses feasibility (scientific and financial), before submission to the COHERE SC for consideration and approval.

The COHERE EC will, on behalf of the COHERE SC, be responsible for communication between COHERE SC meetings with the theme leads, the project teams, the COHERE SC and external experts as needed. It is responsible for organizing the meetings of the COHERE SC. It is responsible for compiling regular reports to EuroCoord, as well as minutes of meetings, newsletters and documents summarizing the status of projects, for the COHERE SC. The COHERE EC meets every two months via teleconference – and more frequently if required. Two to three meetings every year may be face-to-face.

The COHERE EC is responsible for ensuring that any public presentation or manuscript involving findings derived from the use of the COHERE database are appropriately reviewed by all members of the COHERE SC prior to submission and/or presentation. Abstracts will be circulated within the COHERE SC for review at least one week prior to the deadline for submission. The minimum circulation time for manuscripts is 3 weeks before submission. See section 6. Publication Rules.

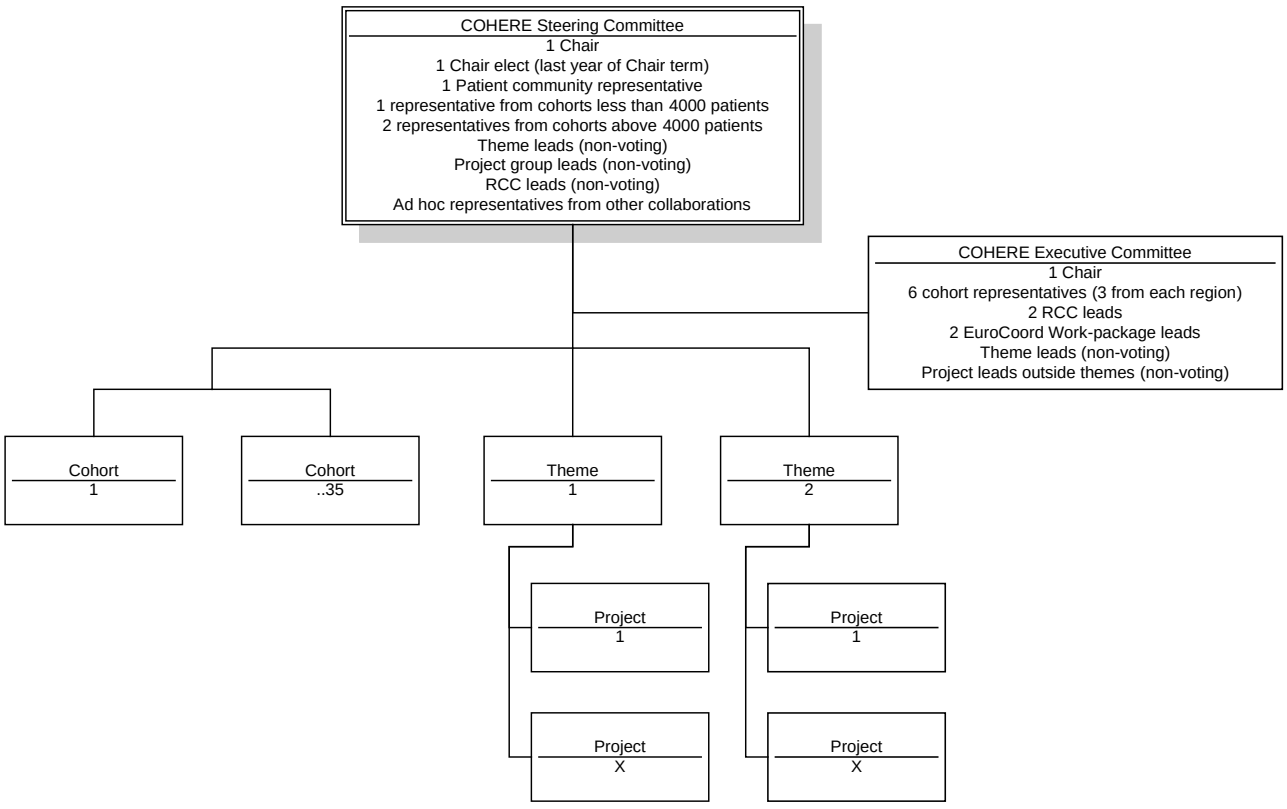

Figure 1. Organizational Structure of the COHERE Steering & Executive Committees

2.2.3. Decision Making Process of the COHERE EC

The COHERE EC in its decision-making operates by consensus. Very occasionally during its business, voting may be required. In such situations, the majority vote will determine the course of action.

However, all major decisions must be presented to the COHERE SC for approval, e.g. issues related to policy development, replacement of representatives, in-or exclusion of cohorts, decisions of financial importance and the like. Likewise, in the case of a split vote in the COHERE EC, the issue will be presented to the COHERE SC for decision.

3. Process of Scientific Proposals

COHERE cohorts, and others interested can propose scientific projects and analyses that address new hypotheses. Priority will be given to proposals from COHERE cohorts. Proposals for projects planning to use the COHERE dataset must first be submitted to the COHERE EC using the template for new proposals (Appendix 7, latest version to be obtained from RCCs) and the data specification form (Appendix 8) and submission follows the below process:

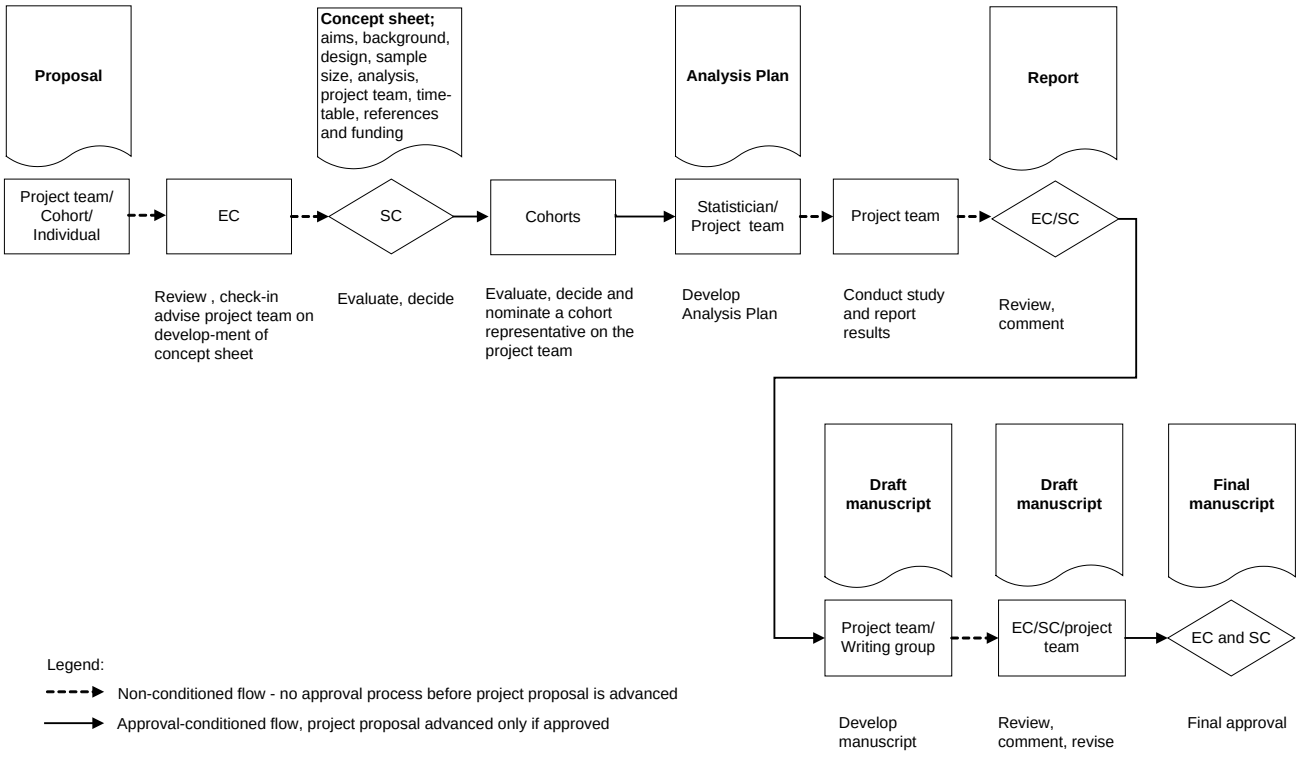

Figure 2. Process for submission and approval of project proposal in COHERE

3.1. Budget management and preparation

Any project that requires additional data (either through questionnaires or additional data downloads) should have a budget. A single institution should ideally hold the budget for any project and the RCCs and third parties would invoice this central fund for expenditure, the spendings being closely monitored by the COHERE EC on behalf of the COHERE SC. This may not always be achievable with a modular funding model, with different funders having their own regulations and mechanisms of administering funds. The next preferred model would be for the budget to be divided between the RCCs and they administer the funding including that to other parties but again being accountable to the COHERE EC. Other models may have to be examined depending on the source of funding but they need to be compatible with what would be regarded as good financial governance (i.e. potentially subject to auditing) and all models need to be approved by the SC.

A budget template is included in Appendix 6 and includes the following activities:

RCCs. The budget should cover the salaries of the personnel needed to implement the project, as well as funding for different services provided by RCCs.

Scientific project. The budget should cover at least the scientific coordination and the statistical analysis.

Participating cohorts. The budget should aim at least at reimbursing the cohorts for the work required to extract the data for the COHERE project. However, the guiding principle is that only data-items actually received by the RCC will be reimbursed.

Two options can be considered:

- reimbursement of dataset extraction: flat rate;
- reimbursement per Case Report Form completed if the project is based on already merged data.

A project involving re-analysis of the existing database may have minimal funding, i.e. statistical analysis and travel to conference for presentation.

To make the budget of any type of project transparent and understandable, all details should be provided to the COHERE SC when seeking approval for a particular project.

3.2. Procedure for project approval and management

3.2.1. Project development

A project lead should inform the COHERE EC of his/her intention to develop a project and/or seek funds, including the targeted source of funding and deadlines. For this purpose, a formal project proposal describing the aims, background, research design, sample size considerations, details of the analysis, membership of the project team, timetable for the work, relevant literature references, funding requirements and dissemination objectives will be used (see template Appendix 7 and 8). Proposals will be reviewed and approved by the COHERE EC before being discussed electronically and/or at meetings among the COHERE SC where the final approval will be given.

The following steps should be taken when submitting a new proposal:

1. Project Lead completes the proposal form (Appendix 7) and data specification form (Appendix 8) and submits to Theme Lead for review (Theme Leads are responsible for maintaining oversight of projects, including ensuring that there is no overlap between a newly proposed project and any existing projects, both within and outside the theme).

2. If appropriate, proposal is circulated to Theme Group with 2 weeks for review and endorsement.

3. Project or Theme Lead submits proposal to Chair and RCC leads and coordinators.

4. Relevant RCC circulates proposal to Executive Committee with 1 week for review.

5. Approved proposals are circulated by the same RCC to the Steering Committee with 2 weeks for review.

6. Unapproved proposals are returned to the Project and Theme Leads for revision.

The project together with a budget should be circulated to the COHERE EC at least 10 working days before any proposed submission of the project to seek funds. This document should then be circulated to the COHERE SC at least 5 working days before submission of the project to seek funds or to be developed.

The allocation of funds for specific projects should be agreed before the project starts. In addition, any proposal should provide a time schedule documenting major milestones such as the initiation of the project, data collection and the production of reports, abstracts and manuscripts. Project specifications including variables and data description will be submitted together with the proposal so cohorts are able to see what data they agree to contribute if they participate.

3.2.2. Theme leads

Theme leads are researchers with interest and track record in the theme field who stimulate the development of projects. For current themes and theme leads, please see Appendix 4.
Theme leads have responsibility for:

1. Working with the COHERE EC, RCCs, and COHERE SC (members of which may have particular expertise) to identify new potential projects within the theme area (and, if necessary, identify potential project leads for new projects which do not yet have a lead person).

2. Taking an overview of the COHERE projects that fall under their theme in order to identify potential areas of overlap between specific projects, and to facilitate resolution of these, involving the COHERE EC as necessary. In some cases, to perform this role in liaison with another theme lead also when there is potential overlap between projects in different themes. This includes monitoring new proposals for projects to ensure they do not overlap with existing projects within the theme. As necessary (e.g. where project leads are not present), representing the projects within the theme at COHERE EC or SC meetings.

3. Taking the lead in compiling (based on input from project leads) reports as necessary on the projects within the theme.

3.2.3. Project Group

A scientific project group, headed by the Project Lead, must be established after the data set has been received. The Project Lead is responsible for conducting the research project and will ensure group members are updated by e-mail and meet (either face-to-face or via teleconference) on a regular basis and as early as possible to ensure that the analyses are progressing as planned and to discuss any methodological issues. Each scientific project group will also report regularly on progress to the theme lead and the COHERE EC via the supportive RCC (for current list of project teams by RCC, see Appendix 11 and for reporting template see Appendix 9). The Project Lead is expected to attend COHERE EC calls prior to the initiation of the project and when issues arise that require discussion. The Project Lead is responsible for securing funding for the project unless otherwise decided by the COHERE EC. The Project Lead suggests the institution where the analysis will be conducted and suggests the person responsible for the analysis for approval by the SC.

Individual cohorts that express an interest in participating in a project are allowed to nominate one representative to the project group. For some projects, where a combination of expertise is required (e.g. virology) two representatives, may be permitted e.g. PLATO II model. Other experts may be co-opted at the discretion of the Lead and project group as required. The project group will have considerable involvement at the time of planning the analysis, at the time of reviewing results for abstract preparation and conference presentations, and during the drafting of the manuscripts. They will see the early drafts of all conference presentations and manuscripts.

3.2.4. Writing group

A writing group headed by the Project Lead will be established. Only representatives of cohorts that have contributed data to the analysis of the project will be members of the writing group as will other members of the project group who have made a significant contribution to the project according to accepted academic standards (e.g. statisticians, other scientific experts) together with a representative from each of the two RCCs.

The COHERE SC prior to implementation should approve the analysis plan for a given project. Analyses that conform to this plan will be conducted in the first place. Only one institution will be provided with a copy of the dataset for the analysis of a given project. Copies of the dataset should not be circulated outside the project leader and the statistician, both of whom are responsible for the analysis – in case of very large projects the responsibility for sub analysis can be delegated to sub project leads and sub project statisticians.

To document the responsibility and lifecycle of the dataset the project lead and the statistician will be asked by the supportive RCC to sign a Data Confidentiality Agreement (Appendix 12). The RCCs will keep a database with details of projects and dataset lifecycle. A checklist related to publication has been developed (Appendix 10), and particular attention needs to be given to the acknowledgement section of the manuscript for which is updated frequently and is available from RCCs. Once the project is completed, the statistical scripts, the final dataset used to generate the analysis and original output leading to the publication(s) have to be submitted electronically to the supportive RCCs of the project for filing within one month of publication. Six months after the time of publication of the last report of the project, all copies of the COHERE dataset at the institution

in which the analysis was conducted, must be deleted (an extension may be granted by the COHERE EC in justified circumstances). One person at the institution conducting the analysis is designated as being responsible for ensuring that these requirements are fulfilled.

Reports/manuscripts agreed by the Project and Writing Groups will be circulated to all members of the COHERE EC and SC by the RCCs for comment and suggestions for a potential target journal at least 3 weeks prior to submission and the proposal's writing group will revise the report, taking account of all written comments wherever possible. The revised manuscript will then be re-circulated to the same group with a brief time limit not exceeding one week for final comments and then submitted for publication.

Abstracts/conference presentations should be based on the pre-agreed objectives of a project approved by the COHERE SC. They will be circulated to the COHERE SC for review at least one week prior to the deadline for submission to the targeted conference. The proposal's writing group will revise the abstract, taking into account all comments wherever possible. The final version will be circulated to the COHERE SC after submission via the supportive RCC and the presenting author will be responsible for informing the SC of the decision of the conference committee. Once accepted, a presentation must be circulated to the COHERE SC for comment at least one week before the day of the presentation. The proposal's writing group must revise the abstract, taking into account all comments wherever possible. The final version will be circulated to the COHERE SC after the presentation.

The COHERE EC, and corresponding theme lead, receive statistical reports, early drafts of abstracts, presentations and manuscripts with the same timing as the writing group. The COHERE SC – or in day-to-day management, the EC, has final decision-making power on the submission on behalf of COHERE of all abstracts and manuscripts, although in reality this option should be avoided if at all possible.

The EC is responsible for ensuring that any public presentation or manuscript involving findings derived from the use of the COHERE database are appropriately reviewed by all members of the COHERE SC prior to presentation or submission. They are also responsible for anticipating conference deadlines and identifying abstracts to be submitted as far in advance as possible.

4. Regional Coordinating Centres

COHERE has established two Regional Coordinating Centres provide the operational infrastructure in terms of administrative, financial, statistical and technical support. The RCCs, oversee the strict adherence to the Manual of Operation and quality assurance formats,RCCs are also responsible for the collection and the compatibility of data from the cohorts linked to their respective regions, and for ultimately merging these data-sets into the main COHERE database. They are responsible for the security of the COHERE database. They manage the communication with the COHERE EC and SC and the maintenance of COHERE's webpage. The current COHERE project groups are administratively supported by one of the RCCs, a list of the current distribution of project groups by RCC can be seen in Appendix 11.

The RCCs are staffed with an RCC lead, study coordinator, data manager, statistician, and administrative/financial coordinator.

The RCCs will assist the project teams at all stages of the design and implementation of specific projects. They relay comments and provide feedback to investigators on scientific proposals and projects. They are partners for the EC for external communication regarding COHERE. They are responsible for overview of project accounts, and financial overview. The RCCs have the responsibility to follow-up with cohorts leads ensuring that the individual cohort has the appropriate ethics approval within existing local and national regulations.

The RCCs are responsible for the joint website maintenance (http://www.cohere.org). This includes descriptions of the COHERE structure, activities and a list of COHERE contacts, status reports, minutes of meetings and standard operating procedures. The website displays results of completed studies, updates on ongoing projects, together with restricted information for partners, such as details of data standardization and new proposals. It is also possible to download all the posters and link to papers published by COHERE. This website is regularly updated to enable wider dissemination of results from COHERE projects.

The tasks of the two RCCs are harmonised,via adherence to the same SOPs. They meet regularly. They share organisations of meetings of the SC and meetings. Additionally, the two RCCs have a seat in the COHERE EC to ensure that these procedures are carried out in complete synchrony.

4.1. Data-management

COHERE performs annual data mergers in the first quarter of the year. The data mergers are planned well in advance to make sure that all data items needed for the analyses planned are considered. For each merger the RCCs prepare a SOP describing the background for the projects for which the merged dataset is to be used, the detailed timing of the merger, eligibility criteria for patients, justification for data needed, data sections and data formats, file transfer to the RCCs, error and discrepancy reporting, national regulations issues and details on the single variable needed (HICDEP format).

For projects carried out as part of the EuroCoord Network of Excellence, COHERE allows data management and data mergers to be conducted as part of the fourth EuroCoord workpackage – this also implies that collaborative requests for data mergers or collaborations with third party cohort collaborations, as part of the EuroCoord Network of Excellence, will be referred to EuroCoord for information.

As a collaborating research network within EuroCoord, COHERE contributes to the central data management, ensuring harmonisation and standardised definitions of data variables captured by the networks with the aim of ensuring that cross-network data mergers of specified variables can readily occur. This will be achieved by creating a EuroCoord dataset as depicted below as well as by an online workspace that will allow for discussion of data formats between data managers, statisticians and physicians and allows sharing of standard operating procedures, protocols and quality assurance checks. Updates of the HICDEP format and quality assurance checks will be published on the public part of the workspace at least every second year, or more frequently if necessary.

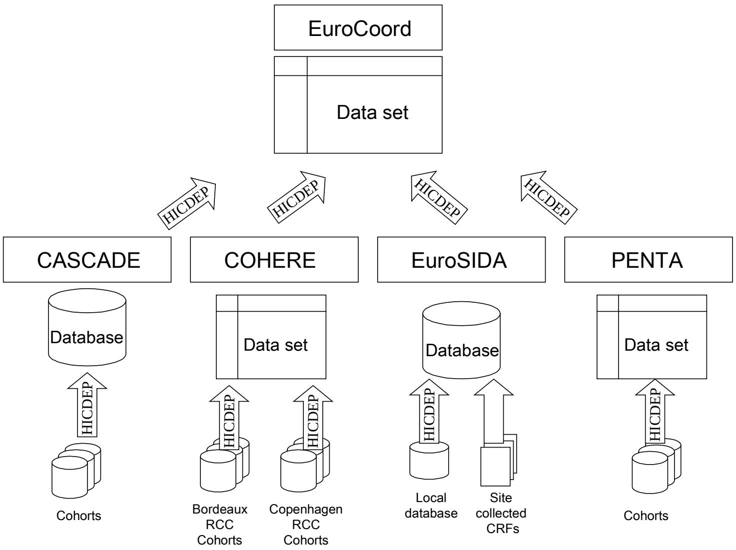

Figure 3. The flow of data from the networks to a common dataset in COHERE, then EuroCoord

Likewise, cross-network data mergers for scientific projects where two or more EuroCoord founding networks are collaborating or data mergers between organisations as COHERE/ART-CC to generate a dataset for a specific analysis will be coordinated. The EuroCoord merger will be performed at a central data management function and will make use of developed data exchange tools that will enable each network to securely submit data via a web based portal and to receive a report of automated discrepancy checks within a few hours. This can be used for direct approval of the submitted data if it passes the established quality threshold, or as a tool for data managers to run quality checks related to a re-submission of data or prior to the final submission of data If the tools are beneficial to any of the individual networks for their internal data merger processes the tools can also be used for this.

In relation to the data merger process, a searchable inventory of available data items and biological material will be created on the workspace. This will allow statisticians and physicians to assess feasibility of new cross-network projects so that cost estimates and need for additional data collection can be readily identified.

4.2. <u>Data quality</u>

The RCCs are responsible for implementing a quality control system and training, and are in charge of preparing and providing the appropriate data extracts of the databases for approved scientific projects. They are responsible for maintaining a log of datasets transmitted to scientific project leaders for analysis and for regularly informing cohorts about the transmission of data to project leaders.

The RCCs of COHERE aim to ensure a high level of credibility of results produced. Methods for enhancing data quality include a quality assurance control program, standardized data processing, careful monitoring of participating cohorts as well as continuous training of personnel.

An SOP for the harmonization of data management tasks at the RCCs was developed and will be made available on the COHERE websites. Further, a data merger platform that runs the quality checks described in the SOP will be made available for cohorts to quality assure their data and

subsequently submit their data to the merger. An annual meeting of data-managers within EuroCoord will be dedicated to the training of key personnel at each of the coordinating centres of the participating cohorts, i.e. data manager and study coordinators. Finally, annual EuroCoord workshops will aim at updating these personnel with the advances of the collaboration, as well as training personnel in specific aspects of quality assurance, data harmonization or data processing.

Active communication between the RCCs and the Cohort Coordinating Centres are used as a tool to promote study adherence, ensure timely transfer of data and training of personnel. RCC data managers conduct cohort visits to document process and gather information about the data quality to better understand the overall COHERE data quality.

4.3. Day-to-day work at the RCCs

The RCC Leads have overall responsibility for ensuring that the SOPs are adhered to during the conduct of COHERE within their region and to secure that the necessary facilities and equipment for the conduct of the activities are present. The day-to-day responsibility is delegated to relevant staff at the RCC and the cohorts in a number of ways:

The RCC *Coordinators* from the two RCCs liaise closely. Within each region, the RCC Coordinator is responsible for the day-to-day coordination with the cohorts and support of project teams within the region and ensure that information relevant to the conduct of COHERE is disseminated in a timely manner to all persons involved within the cohorts. Initiatives within COHERE that require an active role of the clinical site investigators are also funnelled via this line of communication i.e. the collection of additional specific data-items that require access to the source patient records or other information that is not available within the cohort database (e.g. the CoDe standardized data form, the TB standardized data collection form, retrieval of data related to resistance test results, hepatitis, or hepatocellular carcinoma event forms, and resolving queries). When deemed appropriate and to the extent possible, the data-items that are routinely collected within each cohort will be expanded to incorporate data-items relevant to COHERE rather than collecting these data-items via additional routes of collection. The RCC Coordinators in collaboration with the RCC Data Managers are responsible for drafting SOPs for capturing possible new data items.

The RCC *Data Managers* from the two RCCs liaise closely. Within each region, the RCC data manager is responsible for the day-to-day coordination with the cohort data managers of all regional cohorts (the RCC data management team) to complete the tasks outlined in approved projects. Once the data merger is completed within each of the regions, the RCC Data Managers merge their respective databases and create a joined COHERE database for use in analysis of the research projects. Members from each RCC data management team – headed by the two RCC data managers - are responsible for formulating drafts of SOPs for these tasks. RCC DM will alternate leading the COHERE merger (e.g. if the RCC CPH DM led the 2013 merger, the 2014 merger would be led by the RCC BDX DM).

The *RCC administrative/financial* staff from the two RCCs liaises closely to complete the following tasks: within each region, the RCC administrative/financial staff is responsible for the day-to-day coordination with the cohort administrative/financial managers of all cohorts within the region (the RCC administrative/financial team) to complete the following tasks. An agreement may be established between the RCC and each cohort. Payments are transferred following the cohort budget algorithm outlined in the approved budget. Members from each RCC administrative/financial team – headed by the two RCC administrative/financial coordinators - will be responsible for formulating drafts of SOPs for these tasks.

The various project teams are the final components required for a successful function of COHERE. The staff will be organized as outlined in figure 4:

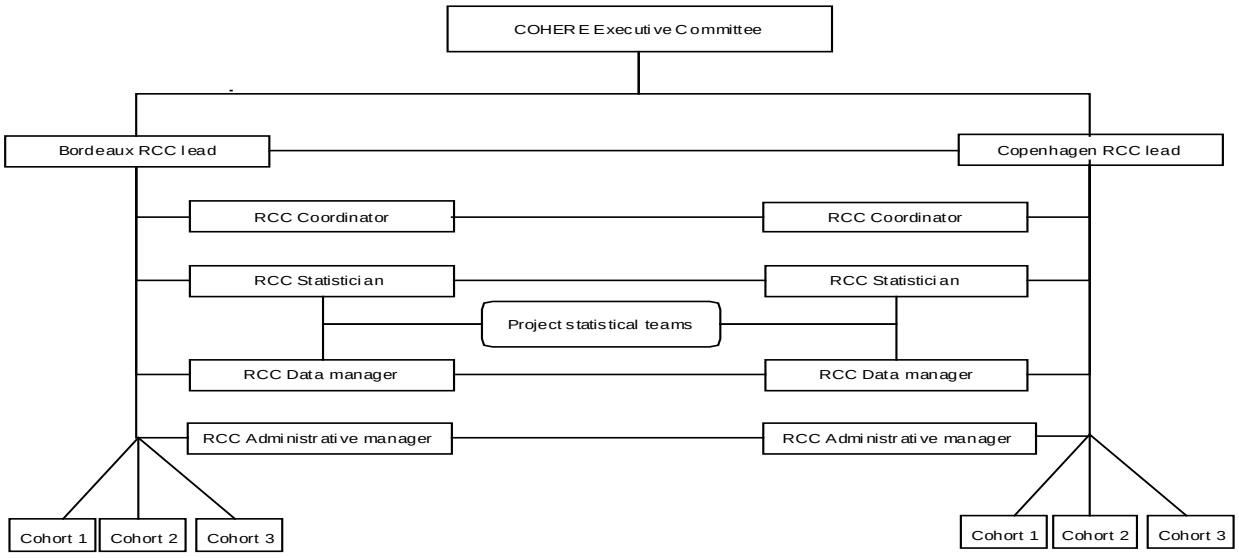

Figure 4. The structure of COHERE responsible for the execution of the research agenda. Within each of the RCC structures, the RCC study coordinator, RCC datamanager and RCC administrator, respectively, supports the theme leadership and the project groups responsible for the single projects.

5. Human Subjects Protections, Privacy and Confidentiality

The COHERE collaboration is a non-intervention data collection study in a representative group of HIV patients from across Europe regardless of gender, ethnic background, sexual orientation, political opinion, religious or philosophical conviction.

As the COHERE collaboration is an academic collaboration between potentially 800 centres in over 30 European countries, it is the responsibility of each investigator/sponsor to follow current national regulations. Of note, the cohorts participating in COHERE have all been in existence for many years, and their conduct is already governed by their required national regulations and guidelines.

For all participating cohorts, the cohort representative and governing body assures that the cohort shall conform to the 1) Declaration of Helsinki in its latest version as it is applied nationally for the conduct of cohort studies, 2) common set of quality assurance procedures developed within COHERE, 3) European Community Directive 95/46/EC on the protection of the individuals with regards to the processing of personal data and on the movement of such data and to the regulation transposing this Directive in national legislation, 4) possible required approval from the competent ethical committee and if required other competent authorities.

5.1. Safety Considerations

Safety issues are not applicable to the COHERE collaboration as no procedures and interventions additional to standard of care treatment are performed for the purpose of the study and there is

no interference with daily clinical care and treatment of the participants, but only collection of information by patient interview as part of standard of care and from patient records.

The research does **not** involve:

- Research activities aiming at human cloning for reproductive purposes,
- Research activities intended to modify the genetic heritage of human beings, which could make such changes heritable,
- Research activities intended to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer.

5.2. Ethics Committee Approval

Prior to any study related activities being performed, Local Ethical Committee approval of the study and procedure for obtaining informed consent from participants will be obtained by cohorts according to local and/or national regulations in all countries participating in the collaboration as well as other national regulatory approvals as applicable, unless no such requirement applies to observational clinical studies according to national regulations.

5.3. Recruitment and Informed Consent

All studies comply with local and national regulations in the country where the cohort is located. Data is collected according to The Declaration of Helsinki as it is applied in the country for the conduct of cohort studies, and the data is collected according to the European Community Directive 95/46/EC on the protection of the individuals with regards to the processing of personal data and on the movement of such data and to the regulation transposing this Directive in the cohort's own country. The data is collected according to all existing ethical and safety provisions applicable in the cohort's own country. If applicable, cohorts have obtained and will continue to maintain approval from the competent authorities required in their operational structure.

5.4. Confidentiality

In particular, Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of personal data and its implementation in national legislation will be complied with for data storage and handling to ensure patient data protection and confidentiality. The above directive will also apply to the handling of samples as well as the conduct of the study.

The confidentiality of all HIV positive persons will be paramount. To ensure this, no names of study subjects will be exchanged or held or other information, which could permit the identification of HIV positive persons. Data released to collaborators and through publications arising will contain no information, which could lead to the identification of an individual..

The data storage, management and handling will be protected in accordance with European Commission Directive 95/46/EC and appropriate national regulations. Under this regulation:

- Data should be sent in confidential form either via registered mail, courier or encrypted data transfer procedure;
- Databases are installed on mirrored disks;
- Daily backups allow recovery of the most recent data in case data are inadvertently lost. These backups are stored in a fireproof armoured filling cabinet;
- All databases are password protected.

Transfer of data from RCCs to a statistician for analysis will be done after a data transfer agreement is signed, via an encrypted data transfer procedure, and only the data required for the specific analysis project will be transferred.

All cohorts protect the identity of their enrolled patients by providing arbitrary identification numbers for the patient, which serves as the identification of the patient.

5.5. Inclusion of women & children

The COHERE collaboration will recruit men and women in the proportions in which they are represented in the participating clinics, so women are proportionally represented in the study. As part of the routine analysis performed gender issues are investigated in order to assess any new developments related to this.

Pregnant women may participate in the study, as no interference with their treatment or pregnancy in any way will take place. Data on frequency and outcome of pregnancy is collected in the study.

Patients will be enrolled by physicians providing primary HIV care in centres that reflect the demographics of the HIV epidemic in their location. There will be no enrolment restriction in regard to gender, race, ethnicity or socio-economic status for any COHERE study. Women will be encouraged to participate and, based upon past history with existing COHERE cohorts and the clinical site populations, are expected to constitute around 20% of participants.

A number of cohorts participating follow the mother-to-child transmission of HIV. These cohorts are located in the Belgium, France, Italy, Spain, Switzerland, and UK. Additional protections are required for the inclusion of vulnerable populations, and the data collected for each of these cohorts adhere to the local and national regulations of the countries where the cohorts in question are based.. All data collection/management should adhere to local and national regulatory requirements for the protection of the privacy of the patient and patient health data.

6. Publication Rules

Cohorts that have contributed data to a specific project are entitled to a representative in the writing group of manuscripts. The acknowledgment section of all manuscripts should follow the rules as outlined in Appendix 10 Publication Checklist and Acknowledgements.

Certain timelines for review of manuscripts/abstracts/posters apply:

Reports/manuscripts

- The Project Writing group will submit the manuscript to the supporting RCC for review by the SC at least 3 weeks prior to submission to the target journal
- The revised manuscript will be re-circulated with a brief time limit not exceeding one week for final comments

Abstracts/conference presentations

- The Project Writing group will submit the abstract/presentation to the supportive RCC for review by the EC and SC at least one week prior to submission to the targeted conference

- The project's writing group will revise the abstract, taking into account all comments wherever possible.
- The final version will be circulated to the COHERE SC after submission via the supportive RCC.
- The presenting author will be responsible for informing the SC of the decision of the conference committee

Approved posters/oral presentations

- Once accepted, the Project Writing group will circulate the poster/presentation to the COHERE SC for comments at least one week before the day of the presentation via the supportive RCC
- The Project Writing group will revise the presentation, taking into account all comments wherever possible. The final version will be circulated to the COHERE SC via the supportive RCC after the presentation

All COHERE publications that are fully or partly a result of funding through EuroCoord must contain the statement:

The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under EuroCoord grant agreement n° 260694.

For the wording for EuroCoord authorship, COHERE will use "COHERE in EuroCoord".

The methods section of the relevant manuscripts, presentations and posters should cite EuroCoord, e.g. "COHERE data were pooled within the EuroCoord network" and this should be followed by providing the website (www.EuroCoord.net). A EuroCoord Acknowledgement description is given in Appendix 10.

All presentations and posters related to EuroCoord should conform to the standardised format for slides and posters and include the EuroCoord, EU and FP7 logos, along with the standard statement acknowledging the EU funding.

Authorship

The project teams must adhere to the authorship rules agreed by the COHERE SC. These rules conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals created by the International Committee of Medical Journal Editors ("Vancouver Guidelines"). Exceptions to these rules can only be allowed by request and the approval of the SC.

The guiding rule for authorship of manuscripts and presentations which are based on the main, pre-agreed objectives of the project containing all or most of the combined dataset, should have a group authorship in the following format "The (name of the project) project team for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord" and the names of members of the Writing Group are to be listed in an appendix (refer to Appendix 10).

Potential abstracts and manuscripts should be noted in project proposals and Project Leads should familiarize themselves with the respective journal/conference authorship rules at this stage in order to identify any potential representational issues.

Authorship rules apply to both manuscripts and conference abstracts with exceptions made on a case-by-case basis. It is recommended that the project group, if it realises that a group authorship is not possible for the target journal, maintain an updated and agreed named author list for easy EC/SC approval related to the actual submission. Requests for exceptions should be submitted to the respective RCC and will not be considered without sufficient justification. Requests will then be circulated to the EC/SC for approval. As this process can be time consuming, requests should be submitted as early in the project as possible.

In many cases, even if journals accept the COHERE group authorship PubMed does not always list the writing group as co-authors. In this case, the writing group leads should contact PubMed to have them list writing group members as authors, which COHERE authors have done successfully at several occasions. In rare instances and in scientific reports specialized in nature (i.e. methodology or novel techniques), named authorships (where members of the team which undertook the analysis and wrote the report are named individually) can be used after authorization by the SC with a format as follows

“Firstperson A, Secondperson B, Thirdperson C, etc … on behalf of the COHERE Study Group”

If after discussion with the journal and PubMed, it remains impossible to have writing group members listed as authors in PubMed, a named authorship approach, as described above, instead of a group authorship can be accepted after approval from the SC.

A named authorship for abstracts submitted to conferences, can either follow the rule for manuscripts outlined above or simply name the Project Lead with a format as follows:

“Project leader for COHERE in EuroCoord”. For all authorship styles:

- It is recommended that the scientific input and the amount of data or the number of laboratory specimens/laboratory results per cohort be taken into account when deciding the order of co-authors within the writing group, e.g. if a cohort contributed 30% of the data, the authorship and acknowledgment of the cohort should be more prominent than if the cohorts contributed 5% of the data. In addition, each contributing cohort with two seats on the COHERE SC may have up to two co-authors within the writing group if their cohort has contributed a significant amount of data to the project, with the possibility for a third author in extreme cases. The cohort must provide justification for requesting a third author, with the final decision being up to the EC. It is the cohort’s responsibility to determine who will serve as co-authors. While authorship issues can never be perfectly balanced, an effort should be made to better represent the effective contribution of the cohort. Project Leads should review the distribution of data to determine who should be involved in the writing group and their authorship position as early in the project development as possible.
- A listing of all members of the SC, key personnel at the two RCCs and other key cohort investigators will also be included (refer to Appendix 10). In addition, the names of all cohorts contributing data to that specific report must appear in the print version together with a link to the COHERE website which contains the detailed acknowledgment sections from all cohorts including their funding.

Collaborative projects follow the same authorship rules as other COHERE projects. All members of the collaboration should be aware of authorship issues at the initiation of the project.

The lead author of a manuscript submitted to a journal is responsible for obtaining Conflict of Interest Declarations and/or Copyright Transfer Agreements from all co-authors. The co-authors on the other hand have a responsibility to respond timely to requests for signature of these forms. If a co-author does not respond within the given timeframe – usually not less than one week – and remains unresponsive after an additional reminder, the lead author can proceed with the publication process, withdrawing the unresponsive co-author after obtaining the COHERE Chair's consent.

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