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Annex 1 to D7.3

Concept for a Study Protocol focusing on Recruitment, Fieldwork and Sampling

WP7

Task 7.2

D 7.3

Version 3.0

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1 Introduction to the Study Protocol

HBM-studies in the sense of HBM4EU are epidemiological studies. According to the International Epidemiologic Association (IEA), "… the [study] *protocol is the cornerstone of any epidemiological research project. In this the purpose of the study, the hypotheses, the design, the source population, and the planned analyses are described. Administrative issues, ethical considerations and possible problems and limitations are also addressed in the protocol" (IEA 2007).*

The IEA also admits that it is not possible to present a standard structure for a protocol that could be used in all situations but all epidemiologic research should follow standards of good scientific practice. Such standards have been published i.e. from the American Chemical Manufacturers Association (Cook 1991) and by the German Society for Epidemiology (DGEpi), last updated 2008 (DGEpi 2008).

A kind of transformation of such guidelines is provided with this Concept for a Study Protocol developed by partners of Task 7.2 of the European Joint Programme HBM4EU. This Study Protocol does not cover all aspects mentioned above by the IEA, it does not have a comprehensive paragraph on the purpose of the study, the state of the art or on hypotheses – these parts could be added and may be important when applying for money and ethical and data permissions.

Task 7.2 provides a template or model for the conduct of human biomonitoring (HBM) studies **to be carried out in the frame of HBM4EU**. Primarily, this Study Protocol covers recruitment, fieldwork and sampling. It is intended to be used for new cross-sectional studies for the adult general population but with some adaptations it can also be used for any other HBM study or HBM part of e.g. health studies. It can also serve to check protocols from already ongoing studies which will be extended with some parts (aligned studies) to deliver comparable results in the frame of HBM4EU (tasks important for aligned studies are especially mentioned).

This template tries to address all steps that are worth consideration when preparing a HBM-Study. It has been developed hand in hand with countries participating in the initiative, taking into account information on existing experience and expertise gathered from the HBM4EU partners.

Previous international studies like DEMOCOPHES have proven that it is feasible to apply harmonised mandatory operational procedures (protocols) in several different participating countries, but a certain amount of flexibility to ensure successful adaptation of the study is needed. To take into account that in a first step for HBM4EU not one harmonised protocol will be followed and also to address the necessary flexibility sometimes alternatives are mentioned for some procedures in the following.

IEA and DGEpi also pointed out that the study protocol should always be available before the study starts to ensure the quality of the study. The study protocol is a compilation of the most important information necessary for the implementation, application, and evaluation of the study. To safeguard validity of data and good data quality it is necessary to follow such guidelines which build the basis for proper study conduct.

A study protocol usually starts with information on the background of the planned study. To serve this, Chapter 2 provides some information on HBM4EU. As it is not possible to prepare one study protocol valid for several studies but to support all who have to design a study, Chapter 3 explains the newly introduced Concept for a Study Protocol, splitting up the procedures for planning a study into five phases (Phase 0 to 4). In the subsequent chapters the different tasks of each phase are explicitly explained, making it easier to keep all necessary aspects for study conduct in mind. The chapters of the Phases 0-4 take over the function of a study protocol, i.e. all aspects which are mentioned in one phase have to be answered and elaborated for the study to be planned.

Please also consider more detailed information in deliverables from other tasks and Work Packages for a full view on important aspects of study conduct, like ethics (Task 1.5), data management (WP10), communication (WP 2 and Task 7.5) and analytics (WP9).

2 Aims of the European Human Biomonitoring Initiative (HBM4EU)

This study (*fill in the name of the study*) is designed to be conducted in alignment with the aims of the European Human Biomonitoring Initiative (HBM4EU). HBM4EU is funded by the European Commission under Grant Agreement No. 733032.

The overall objective of this study should always be in line with one or more of the following, overarching objectives as set out in the HBM4EU Description of Action Section 1.1:

i. Harmonise procedures and tools for HBM at EU level;
ii. Provide and, where missing, generate internal exposure data and link this data to aggregate external exposure and the relevant exposure pathways;
iii. Develop novel methods to identify human internal exposure to environmental and occupational chemicals and establish the causal links with human health effects;
iv. Provide policy-makers and the general public with science-based knowledge on the health risks associated with chemicals exposure; and
v. Improve chemical risk assessment in the EU through the effective use of HBM data.

HBM studies performed under HBM4EU shall fulfil the overarching objectives of the programme, the harmonisation of procedures and tools for HBM methods at EU level as well as the generation of new and gap-filling representative exposure data. The aim is to provide policy-makers and the general public with science-based knowledge on health risks associated to chemicals exposure.

3 Phases Concept

Planning representative HBM-studies usually involves several organizational issues, the order of which is important to respect. A well-developed concept providing a good overview as provided with the Phases concept here can help keeping track of schedule and key players.

The idea of the Phases concept is to split up the planning and conduct of a study into different phases (planning, preparation, concretization, start, and fieldwork). Table 1 presents a rough overview which is explained in short hereinafter:

We discriminate between the Planning Phase (**Phase 0**) where all decisions for the study to be conducted are taken. This is followed by the Preparatory Phase (**Phase 1**) in which all necessary documents are prepared and lacking information is collected. In the following Concretisation Phase (**Phase 2**) the decided issues are started to be turned into practice, e.g. material bought or labs contracted. In the Starting Phase (**Phase 3**) first contacts for getting addresses are arranged; personal contacts and participant involvement follow in **Phase 4** (Fieldwork Phase).

Table 1 gives an overview of possible phases of a (HBM-) study and their characteristics to enable a smooth organisation. These Phases involve mandatory characteristics for new studies and optional characteristics for aligned studies – depending on the state and structure of the study to be aligned. Actually, some issues of single Phases may partly overlap. It is also possible to integrate more instruments than only questionnaires and urine/blood sampling e.g. sampling of drinking water. These additional instruments also have to be considered in each of the Phases.

Table 1: Phases of a study and its characteristics in general

	Characteristics
0 – Planning Phase	**General decisions** on: Study design, samples and biomarkers, participants, fieldwork, data management, budget
1 – Preparatory Phase	**Prepare Study Protocol** and **start to prepare a Fieldwork Manual** including SOPs for recruitment and quality assurance
	Prepare (and test) **questionnaires** (necessary for ethics) and **prepare an Interviewer Manual**
	Prepare analytics
	a) *identify labs* with adequate limit of quantification for selected substances and with successful results in the HBM4EU ICI/EQUAS scheme
	b) *check lab needs* regarding volume/amount of sample, conservation, time required for analysis, contract conditions, etc.
	c) *elaboration of Standard Operating Procedures (SOPs):* All steps and materials required should be described in detail in the corresponding SOPs: for sampling, for sample conservation, for sample reception (including acceptation and rejection criteria), for aliquoting and for biobanking
	Prepare data management (necessary for data protection)
	a) for address holding and handling
	b) for tracking recruitment attempts
	c) for results of questionnaires and analytics
	Prepare communication material:
	a) to get in contact with contact persons for approaching potential participants (registration offices, school principals, etc.) (necessary for ethics)
	b) for all contacts to potential participants (necessary for ethics) including non-monetary incentives like information material, personal results letter, books/bags/toys with study logo
	c) to inform the community / general public
	Apply for **authorisation**
	a) Ethics Committee
	b) Data protection agency
2 – Concretisation Phase	**Finalise the Fieldwork Manual** including communication material, all SOPs and questionnaires
	Engage and train qualified field staff (interviewers)
	Prepare/organize and buy **material**
	a) for the sampling and aliquoting of the matrix to be collected
	b) as incentives/other measures to increase participation rate
	c) for the field staff
	Fix timing of fieldwork (start/end/route plans)
	Contract labs for substance analysis

3 – Starting Phase	**Get addresses** of potential participants (as decided in Phase 0) **Inform the general public** at the sampling location about the study **Inform the labs** of the near start of the study If appropriate: **Acquire rooms** as examination centres at the selected areas (sampling locations)
4 – Fieldwork Phase	**Invite potential participants**, clarify their inclusion, fix an appointment, provide material to collect samples (**Fieldwork I**) **Involve participants in the survey** (interview, examination, samples, incentives, results) (**Fieldwork II**), mainly done by field staff. Quality assurance and control measures are included.
Subsequently	Sample analysis, combine results from questionnaires and chemical analyses, sign data transfer agreement and transfer data to secure server for storage and detailed data exploration, storage of biological samples (biobank), publications etc.

When a country considers to conduct a new HBM-study first general decisions have to be made, e.g. concerning the study design, the participants and how to select them, how fieldwork shall be organized and what does it comprise of, which analytics (substances, biomarkers, matrices, volume and amount) shall be performed and, last but not least, which budget can be spent (this mostly is a prerequisite to decide on all other aspects). When these decisions of **Phase 0** – the Planning Phase - have been made (and this will definitely take a while!), the preparations of the concrete instruments can start (**Phase 1**, Preparatory Phase).

HBM-studies always need to be approved by an ethics committee and the data protection authority, but to be able to approach these authorities, questionnaires, communication material and a data management plan have to be intensively thought of and prepared because the authorities want to approve these materials (changes in format may still be possible). And maybe, before finalizing the materials, they should be streamlined with a corporate design and a logo for all the documents which may be developed. A Study Protocol and SOPs (for analytics and quality assurance of fieldwork) have to be prepared and the preparation of a Fieldwork Manual started. If questionnaires are developed (or translated) an Interviewer Manual which informs about the background/rationale of each question should be prepared. The information collected for the Interviewer Manual is also a good basis for preparation of the communication material for the participants. Conducting a study is rather complex: responsibilities for the single steps and issues have to be defined and assigned to selected persons, even a subcontract for several tasks is possible.

After these responsibilities have been settled, the Concretisation Phase can begin (**Phase 2**, Concretisation Phase), i.e. field staff (interviewers, if a face-to-face interview is planned) have to be hired and trained on all instruments. To conduct a study in a validated manner a Fieldwork Manual, consisting of blueprints of all necessary documents and clear descriptions of all instruments has to be finalised in Phase 2 and provided to every member of the staff. Devices and materials needed to be handed out to the participants or to the field staff or they have to be ordered and stored and the definite timing of the fieldwork has to be fixed and route plans elaborated.

Now the study is ready to start (**Phase 3**, Starting Phase), i.e. recruitment of potential participants begins with acquiring their addresses, e.g. from population registries. If required, rooms as

examination centres have to be rented and communication on the study to the general public can be launched.

After that, the real fieldwork starts with the direct contact to the individual participants (**Phase 4**, Fieldwork Phase). The first part of fieldwork (Fieldwork I) comprises individual contacts to potential participants (invitation, checking inclusion criteria, fixing appointments and sending sampling materials). The second part of fieldwork (Fieldwork II) includes working with the participants from the moment they really participate in the study, e.g. when they answer questionnaires or provide samples and receive their individual results. These procedures are accompanied by quality control measures to warrant high quality of the received results. When fieldwork is finished and samples analysed (which can already start parallel to Fieldwork II if the fieldwork takes some time) all data is subsequently assessed.

For **biobanked samples**, the Phases split up as described in Table 2. D7.2 delivers a strategy and SOPs for human sample exchange, including ethical demands.

Table 2: Phases of a study using biobanked samples and its characteristics

	Characteristics
0 – Planning Phase	HBM4EU decides on **suitable biobank material**, **inclusion and exclusion criteria** in relation to chemical of interest, sampling and **storage conditions**. **Permission** from biobank responsible person/PI has to be granted
1 – Preparatory Phase	**Check availability of informed consent** (IC), does this cover transfer of samples within EU or outside EU? Or is a new IC needed?
	If appropriate: **Prepare communication material** for seeking new informed consent from participants
	Prepare data management files: sample and information coding and results
	Gather information associated with the biobanked samples
	Use questionnaire to collect basic information in a harmonised manner (pre-specified requirements defined by tasks: 7.2, 8.2, 11.2, 13.2) on e.g. study design, time frame, sampling material, questionnaire and additional relevant information
	Reassure sample and data availability according to inclusion criteria and research question, and within a defined time frame
	Apply for ethical approval (if not yet available) and **data protection**
2 – Concretisation Phase	**Buy suitable material for aliquoting** of biobanked samples (if needed), (Recommendations see Deliverable 7.3 SOP on sampling material)
	Appoint analysing laboratory, considering the results of the HBM4EU ICI/EQUAS scheme (subcontract needed?)
	Set up time schedule for sample withdrawal from biobank
	Get signatures for the sample and data transfer agreements (according to D7.2 Annex 1 (SOP 4))
3 – Starting Phase	**Transport to predefined lab** (according to Task 7.4 SOP on sample exchange, see D7.2) including documentation of transport conditions
	Transfer sample related data to study PI and data manager
4 – Fieldwork Phase	For samples already in a biobank there is no fieldwork
Subsequently	**Perform chemical analyses** in laboratories with successful results in the HBM4EU ICI/EQUAS scheme
	Transfer analytical results to data manager (HBM4EU repository)

Specific Phases for **aligned studies** are described briefly in Table 3:

Table 3: Specific Phases of an aligned study and its characteristics

	Characteristics
0 – Planning Phase	**Identify suitable ongoing studies** (Task 8.1A) which include basic requirements for HBM4EU studies
	If suitable ongoing study is identified: **Define the type of extension needed** (new and/or additional biological samples, additional information from questionnaires, registers or clinical examinations)
1 – Preparatory Phase	**Seek permission** from responsible person/study, this needs to be granted
	Determine if additional HBM samples and/or information (questions, examinations) can be collected. If yes, follow procedures for new studies (from Phase 1 or 2 onwards)
	Additionally: **Inform staff and study participants** of the proposed extension

In the following Phases 0 to 4 are described in detail.

3.1 Phase 0: Planning Phase

The Phases concept starts off with a Planning Phase addressing all decisions that have to be taken in advance pertaining different elements of the study like study design and biological samples, selection of participants, recruitment and fieldwork.

All actions the following phases require need to be considered and their execution decided upon already well before the study can start.

General topics to be decided upon are listed in Table 4. A detailed explanation of these general topics follows closely after.

It is important to consider the **conduct of a pilot study** to try out the instruments defined in the Planning Phase. A pilot study tests the feasibility of methods on a smaller scale in order to adjust processes or study material for the main study.

Table 4: General topics to be decided on in Phase 0 of a study

1. Study design and biological samples	• **Aim for representativeness (sample size)**
	• Type (cohort, case control, cross-sectional?)
	• Timing, Duration, Follow up?
	• Substances and their biomarkers
	• Matrices, sampling time (first morning urine/24h ?)
	• Sample volume
	• Biobanking
	• Ethics and data protection
	• Data management
2. Selection of participants	• Target population
	• Sampling frame
	• Geographical distribution
	• Inclusion / exclusion criteria
3. Recruitment and Fieldwork I (individual recruitment)	• Communication
	• Approach to address holder
	• Method and frequency to approach participants
4. Fieldwork II (investigation of participants)	• Instruments to be applied (Questionnaires, Samples (blood, urine, indoor air, drinking water, etc.))
	• Place of direct contact to participants
	• Questionnaire(s) application
	• Sample collection and further processing including sample conservation and shipment
	• Selection of the laboratory
	• Incentives

3.1.1 Phase 0: Study design

3.1.1.1 Representativeness

To achieve European representativeness within HBM4EU it is important that studies conducted in the participating countries also build upon representative samples. Decisions have been taken regarding the way how European representativeness shall be obtained within HBM4EU (Details please see Chapter 4 “Strategies for recruitment and sampling to attain EU representativeness” in D8.1). The way to obtain a representative sample depends among others on the target population. Table 5 lists the best ways to achieve a representative sample in different population groups.

Table 5: Methods for obtaining a representative sample in different population groups and their sampling frames

	Sampling frame (to select from the list of…)	Methods for obtaining a representative sample
General population of adults with or without children or only children (separated by gender and/or age)	Population register (country, regional)	1) Perform random sampling, keep track of non-responders and drop outs 2) Extract from ongoing study
Vulnerable population (pregnant, newborns, seniors, etc.)*	Patient files of clinics/doctors/midwifes	Perform random sampling, keep track of non-responders and drop outs
Occupational population (partly)	Employment records, branch organisations, large cohorts	1) Prepare a list of eligible sampling units (work places) for random sampling 2) Extract from large database/cohort
Children /adolescents (different age groups)	Kindergartens/day care centres, or their groups	Prepare a list of eligible sampling units (schools, day care centres) for random sampling
	Schools, vocational schools, or classes	

*Very often vulnerable populations are contacted directly, e.g. pregnant women when they arrive at the clinic before delivery. This approach is susceptible for selection bias if it is not taken care of that the selection of the premises to be approached were selected randomly (or fully) and that statistical procedures are regarded. See also 3.1.4.3 Sampling frame.

3.1.1.2 Type of study

Decisions on the type of the study have big implications on each aspect of the study conduct but also on the scientific significance especially if elucidating causality is aimed at. In the timeframe given for the HBM4EU project it only seems feasible to conduct cross-sectional studies which include the possibility of a longitudinal follow-up. Cross-sectional studies provide a snapshot of the exposure or health experience of a population at a specified time and are therefore often used to describe patterns of disease occurrence (Kleinbaum et al. 1982), i.e. cross-sectional studies provide information on exposure and disease frequency at the time of the sampling.

In the 2011 pilot study DEMOCOPHES that tested the feasibility of a pan-European HBM study the cross-sectional study design was already used (Joas et al. 2012, Den Hond et al. 2015).

Given the general knowledge and experience with the conduct of cross-sectional studies gathered in the HBM4EU consortium combined with the restricted time frame and the fact that this type of study design allows for representative results which can answer to some raised policy questions, a new study under HBM4EU should be preferably planned as a cross-sectional study.

Biobanked samples can be taken from different kind of studies, cross-sectional studies, cohorts or case-control studies (just to mention the main study types). The same accounts for studies to be aligned. For biobanked samples, D7.2 should be considered.

3.1.1.3 Timing and Duration

The point in time at which a study is started and how long its phases will take (especially the fieldwork) has implications for the representativeness and for organizational aspects of the study. There are some alternatives listed in Table 6. Most favourable for calculation of reference values or other types of data analyses is including seasonal variability possible in longer lasting studies. Studies just covering one season may provide biased results and may need more personnel if many participants shall be included. Studies may also foresee a follow-up some months or years later (even though exceeding the time frame of the HBM4EU project).

Table 6: Alternatives for the timing and duration of fieldwork within a study

	Alternatives	Pros	Cons
Timing/ Duration of fieldwork	Within one season	No seasonal bias; early results	Organisational effort in case of many participants and face-to-face interviews
	Covering some seasons	Organisation convenient for field staff	Seasonal bias
	Covering all four seasons	Seasonal bias can be avoided through logistic measures and a long fieldwork phase	Long lasting study; organisational effort due to length of study

3.1.1.4 Ethics and data protection

To ensure compliance with ethical standards, it is mandatory to submit a proposal for the conduct of each planned study to an ethics committee. Further it is mandatory to ask for permission of the data protection authority. The planning of the study (done in Phase 0) has to be in accordance with the ethics committee and the data protection legislation of the participating countries and their requirements have to be taken into account, as well as the EU General Data Protection Regulation (GDPR, Regulation (EU) 2016/679). It is important to inform that data and results will be shared within HBM4EU pseudonymised at individual level and also in anonymised form (see paragraph on data management below). Each ethics committee and data protection agency has its own rules of procedures and templates which have to be followed. The application process can be rather long (four weeks to several months), therefore it is recommended to approach the relevant authorities early in the planning phase. Within HBM4EU it is mandatory to provide the documents of ethics approval to Task 1.5 as early as possible to make the individual data available for HBM4EU.

An important document for ethics approval is the informed consent which the participant (and/or the legal guardian) has signed to ensure his/her assent to the procedures. Task 7.5 has provided a template for the informed consent ensuring compliance with the requirements on European level by HBM4EU (see Deliverable 7.4).

The following documents, prepared by Task 1.5, have to be considered for any studies under HBM4EU:

- D1.5 Legal and Ethics Policy Paper,
- D17.1 – D17.6 Ethic requirements (see Grant Agreement number 733032; page 111 of 128),
- First, second and following Ethics reports (see internal webpage work package folder/scientific and administrative management/WP1).

3.1.1.5 Data Management

Data management is an important part of each study which includes several decisions about the way how data shall be managed and processed. Studies in the frame of HBM4EU agree to share their data within HBM4EU. Therefore Task 10.1 has developed a **Data management plan** (DMP) which has to be followed. The DMP describes the data management life cycle for all datasets to be collected, processed and/or generated by the research project (to be reached via https://www.hbm4eu.eu/data-management/). As a separate attachment to the DMP, the HBM4EU data policy has been designed. **The procedures described in the HBM4EU data policy shall be followed by all members of the consortium** and ensure that data on human subjects are transferred and used in a secure setting; that use of the data is compliant with ethico-legal requirements (including signed informed consent, ethics approval, and the applicable data protection laws, furthermore the EU data protection regulation, which is applicable from May 2018);

and that the use of both existing as well as new data occurs in agreement with the Data Controller (when applicable, for personal data) or Data Owner/Data Provider (in other cases). Management of datasets that include personal information and health information of study participants will be compliant with the General Data Protection Regulation (GDPR, Regulation (EU) 2016/679). The GDPR is a regulation by which the European Parliament, the European Council and the European Commission intend to strengthen and unify data protection for individuals within the European Union (EU). It applies for the exchange and use of personal data. Anonymised data are not considered personal data, while non-anonymised (including pseudonymised) data are. Hence, the HBM4EU data policy discriminates between the sharing of anonymised and pseudonymised[1] data.

Sharing of data includes exchange of data within HBM4EU. When possible, it is preferred that data are anonymised before exchange. When anonymisation is detrimental to the study and/or to answer the research question, the established procedures to exchange non-anonymised data, i.e. personal data, shall be followed. To reduce the risk of re-identification, it is requested that such data are at least pseudonymised before exchange.

Anonymised data – IPCHEM portal website

The **IPCHEM portal website** (**https://ipchem.jrc.ec.europa.eu/**) enables to search, access and retrieve **anonymous chemical occurrence data**. It is possible to share the data either with the general public or with subsets of users (user groups). Possible user groups are HBM4EU project group[2], EU Commission and EU Agencies, EU National bodies, and General Public. More information on the user groups can be found at the IPCHEM portal website[3].

If a user group is granted access:

- All members of the group can use the data for any purpose they want
- No agreement between data provider and data user for downloading and using the data[4].

Pseudonymised data – HBM4EU repository

To exchange pseudonymised data within HBM4EU, the **HBM4EU data repository** (https://ipchem.jrc.ec.europa.eu/share/) shall be used. The HBM4EU data repository is part of the IPCHEM platform and ensures save transfer, storage and access of the data. It is highlighted that, according to the GDPR, sharing of non-anonymous data – and hence pseudonymised data - requires a specific prior **agreement between the data controller[5] and the data processor[6]**, stipulating the rights and obligations of both parties**.** Template agreements are currently under revision and will be shared soon via https://www.hbm4eu.eu/data-management/. The legal framework to ensure that the transfer of pseudonymised data by the Data Controller to the HBM4EU repository is GDPR compliant is currently being established.

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[1] Pseudonymisation means the processing of personal data in such a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

[2] The option to make the data on the IPCHEM portal website accessible only to HBM4EU project group follows indications of Articles 10 and 11 of the IPCHEM Data Policy and related to "Use of IPCHEM for projects on chemical monitoring data".
This extraordinary project-specific accessibility rules can only last temporarily for the duration of the HBM4EUproject. Upon the dissolution of the Project the data generated, collected or analysed in the course of the Project will have to be made accessible to IPCHEM User Groups according to the Open Data Principles and the Exceptional Accessibility Regimes described in Articles 4-7 of the IPCHEM Data Policy.

[3] Article 5. IPCheM User Groups" of "IPCheM – The information Platform for Chemical Monitoring: Data Policy, Date: 25/07/2016 , Version:2.3.

[4] However any user "shall acknowledge the source of chemical monitoring data retrievable through the IPCHEM platform whenever such data are used", according to Article 12 of the IPCHEM Data Policy.

[5] The Data Controller is the person who determines the purpose and means of the processing of personal data.

[6] The Data Processor is the person who processes personal data on behalf of the Data Controller.

The Data Controller is responsible for the pseudonymisation process and for ensuring that directly identifiable variables are not transferred to the HBM4EU repository. Directly identifiable variables include – but are not limited to – national ID number, name, phone number, e-mail address, address, geographical coordinates (at a resolution that allows re-identification of study subjects). One shall also be aware that a combination of just a few indirect identifying variables (such as birth data, gender, and zip-code) can be sufficient to re-identify an individual in a dataset. In this context, the Data Owner/Data Provider shall only provide such variables at the lowest possible resolution that is necessary for analysis, e.g. district instead of zip-code; year of birth or age instead of birth date. The HBM4EU codebook (section: Data Format) has implemented such strategies to reduce the risk of re-identification.

In case the study coordinator is not a data controller, contact details of the data controller(s) need to be provided.

In well justified cases, one can opt to use the HBM4EU repository to share data that are not subject to GDPR legislation (aggregated data, anonymized single measurement data). In that case, the data owner or mandated data provider shall notify the IPCHEM Team (ipchem-support@jrc.ec.europa.eu) by sending the identity of the people that shall be granted access to the data. In case an agreement between the data owner and the data user is desired, the data provider is responsible for establishing one (templates are not foreseen by HBM4EU).

Data Format

Metadata of all HBM data sets used in HBM4EU must be integrated in the IPCHEM portal website and made accessible to all user groups to ensure that the datasets are findable. The metadata shall be provided by filling out the **HBM4EU IPCHEM metadata template**.

For **anonymised** as well as for **pseudonymised data** it can be opted to provide data in **own format or in HBM4EU format**. For HBM4EU co-funded data, single measurement data and aggregated data are to be transferred in **HBM4EU format** using the HBM4EU data template and analysis script (R) respectively. This will enable comparison between data collections and between analyses. Only the transfer of additional variables that may be needed to answer a specific research question is allowed in **own format**

Guidance, templates and an example are provided via https://www.hbm4eu.eu/data-management/.

3.1.2 Minimal requirements considering the sharing of HBM4EU co-funded data

Data Providers shall complete the Data Transfer Form, in order to indicate the format of the data and the conditions under which they agree to make the data accessible via the IPCHEM portal website and via the HBM4EU repository. Table 3 **in D7.3 (main document)** provides a pre-checked table with the minimal requirements for sharing of HBM4EU co-funded data. The data controller commits him-/herself to have established the necessary to enable this.

In the Planning Phase of a study it is important to note – as stated above - that data generated within HBM4EU and for which HBM4EU co-funding is used to generate them, shall be made available for HBM4EU research (across all pillars and WPs) as single measurement data (individual records) and shall be made available to policy makers upon request. Together with the chemical measurement data, the accompanying variables that are needed to enable dedicated analysis shall be made available as single measurement data. These requirements shall be taken into account when applying for ethics approval and (when applicable) data protection approval to ensure that they can be fulfilled. The HBM4EU data transfer form shall be completed and submitted together with a filled out metadata template (HBM4EU harmonized). Data generated with HBM4EU co-fund shall be uploaded (in accordance with the HBM4EU codebook) to the

HBM4EU repository through which they are made accessible to other HBM4EU consortium partners. When using HBM4EU-cofund, the data controller shall ensure that this is possible. Access to and permission to use the data is only permitted upon data controller – data processor agreement. The latter is the entity performing analyses on the data on behalf of the data controller. The most important points of this agreement are:

1. A description of the data (i.e. the compilation of the metadata fiche);
2. A clear specification of the use of the data that should be in line with ethical permissions;
3. The duration of the processing;
4. List of required variables;
5. Description of the subset of the data: (e.g. specific age range, sampling period)
6. The commitment of both parties to work GDPR compliant;
7. A description of organisational security measures, and a commitment to destroy or handle the data back to the controller after the processing;
8. Identification of the people that shall be granted access to the data in the HBM4EU repository, to enable access based on EU id.

All information and templates regarding HBM4EU Data Management are available via https://www.hbm4eu.eu/data-management/. The helpdesk on data management is available to support and advice you in data management related tasks of WP10 (internal webpage: https://www.hbm4eu.eu/privatehelp-desks__trashedwp10-help-desk/).

3.1.3 Phase 0: Biological Samples / Analytics

In the Planning Phase decisions on the substances of interest have to be taken. Part of this decision has already been taken by HBM4EU. In a first prioritization round in 2016/2017 HBM4EU has prioritized 9 substances/ substance groups for which European data is needed:1) Phthalates, DINCH; 2) PFAS; 3) Flame retardants; 4) Cd, Cr; 5) PAHs; 6) Anilines, MOCA; 7) Bisphenols; 8) mixtures and 9) emerging chemicals. A next prioritization round runs in 2017/2018. (New) surveys shall be conducted to fill identified data gaps. Countries still have to decide which of the substances they want to analyse. The selected substances determine the matrix (urine, blood, etc.), the volume of the matrix needed for one analysis (regarding the intended LOQ) or even the sampling time (substances with short or long half-lives). Further decisions pertain the whole volume of the matrix collected from the participants, sampling vessels and the number of aliquots to be derived and analysed or stored and the number of fieldblanks to be taken.

All these decisions have main impact on the fieldwork, the questionnaires and even the study design. Depending on the half-live of the target chemical in the selected matrix the time of sampling (morning / evening; distance of time to last meal) for that matrix should be taken into account, and this way it can have consequences to the way fieldwork should be scheduled. The decision on the necessary number of participants for a representative sample is based on statistical power calculations and therefore based on the selected substances.

It also has to be decided what happens with the samples in the field (directly send to a lab (which lab?) or handled/stored at the sampling location). In the Planning Phase also decisions on the material of the tubes and sampling bottles have to be made. Also, conservation of samples during and after fieldwork and transport conditions to the laboratory or biobank have to be taken. Some recommendations on such decisions are provided in Table 7.

Table 7: Recommendations for material for sampling and aliquoting

	Recommendations
Material identification	Dependent on: the biological matrix and the target analyte, the volume / quantity of the sample, etc. Advise: check the possibilities available in the market (the material of which is made of, the size, cost, availability, etc.)
Material selection	Considerations: the additives to preserve the sample, avoid specific material depending on the target chemical, test background contamination and/or take precautions if necessary, etc.
Aliquoting	The same recommendations as for the sampling material and additional ones: • ensure the material stability during the storage in the conservation conditions. • check stability of the samples during the conservation • check the quality of the labels identifying the frozen aliquots • define the proper volume of the aliquots to avoid unnecessary freeze/thaw cycles.

A decision has to be taken where the analyses of the collected samples shall be performed, which are qualified labs for the selected substances. For projects in the frame of HBM4EU samples should be analysed in laboratories that achieved successful results in the ICI/EQUAS scheme provided by WP9. Additionally, if the laboratory is not a member of the HBM4EU EJP it will be necessary to make use of subcontracting.

Within HBM4EU WP9 is the counterpart for analytical issues, please see specific deliverables. Some SOPs for pre-analytical aspects concerning sample taking are attached to Deliverable 7.3 as part of the Fieldwork Manual.

3.1.4 Phase 0: Selection of participants

A Study Protocol needs to provide information on the selection process on participants for the respective study.

Within HBM4EU the selection of participants follows developed guidelines taking already existing data of HBM4EU partners on the first priority substances into account. The next paragraph describes the selection process for HBM4EU on EU level.

3.1.4.1 Selection of countries and target population within a country

To set up a multistage probability sampling method in EU, **each participating country in HBM4EU is set as a primary sampling unit (PSU)**. To attain an entire European coverage within HBM4EU, a European maximal scenario would be sampling in each of the participating EU countries. To ensure sampling feasibility and due to financial constraints, the number was reduced to 12-15 European countries. These countries need to be distributed over all geographical regions in Europe. **Four geographical regions (clusters)** are defined according to the United Nations geoscheme for Europe: Northern Europe, Eastern Europe, Southern Europe and Western Europe.

The sampling domains for which at least specified reliability is desired in Europe are **gender and age groups**. The seven age groups that are targeted within the HBM4EU surveys are: 0-2y, 3-5y, 6-11y, 12-19y, 20-39y, 40-59y, 60-79y.

In each participating country, and for each of the selected age groups, we propose to **include 150 male and 150 female participants**. The sample size was chosen to ensure also inclusion of participants from different socio-economic strata and from different community sizes (urban, suburban, rural). To include different socio-economic classes, education level can be used as a proxy (International Standard Classification of Education (ISCED), which includes 9 levels of education (ISCED 2011, see task 7.2 report). The sample size is indicative and may need further adjustment for the specific chemical group because of expected population variability of the biomarker. Considering the geographical locations, inhabitants from urban, suburban and rural

areas are accepted. Hot spot areas, with known historical/actual environmental contamination need to be excluded.

In summary: to calculate EU reference values samples and data are collected in minimally 12 countries, with 3 countries per geographical region. Per country and per age group 150 males and 150 females are included. This results in minimally 3600 EU participants. Other possible sampling schemes are shown in Table 8. The schemes are applicable to newly collected as well as biobanked samples. In Task 8.1 EU study alignment will be done for the EU-wide exposure assessment to the HBM4EU priority substances to be measured in specific age groups among 12 countries over the 4 EU geographical regions mentioned above (scenario on 3rd line of Table 8).

Table 8: Possible sampling schemes for HBM4EU surveys, tailored to specific objectives.
The strategy which we recommend, is indicated in red with an asterisk (*). (SSU: secondary sampling unit i.e. province, city, municipality, etc.) (also see updated Deliverable 8.1)

Scenario	No of countries	Sex	No of age groups	No per subgroup	Total number of participants
Objective: sampling frame to assess exposure in Europe or difference between countries/regions					
Actual EU-wide exposure in all age groups (complete scenario)	26	2	6	150	46,800
Actual EU-wide exposure in all age groups (reduced scenario)	12	2	6	150	21,600
Actual EU-wide exposure in specific age group (*)	12	2	1	150	3,600
Objective: Time trends follow-up					
Time trends follow-up in Europe	12[a]	2	1	150	3,600
Regional time trends follow-up (*)	4 SSU[a]	2	1	150	1,200
Objective: Impact of policy					
Impact of policy within a country	1 (before & after)	2	1	150	600
Impact of policy differences among countries (*)	3 (no, median, strict policy)	2	1	150	900

[a] *with the precondition that for the selected country/SSU at least two previous time points of exposure data are already available.*

(*)*the sample size for representative sampling needs to be adjusted according to the samples sizes needed for the specific chemical group because of expected population variability of the biomarker.*

3.1.4.2 Inclusion/exclusion criteria

As mentioned above, 300 individuals, from each of the age groups, including males and females need to be recruited from the general population (exclusion of hospitalized individuals). No further general inclusion and exclusion criteria are set for studies in the frame of HBM4EU. However, for specific biomarker measurements, additional recruitment and sampling conditions may be set out. Furthermore, following minimal information needs to be collected (in the basic questionnaire), to have an indication of the population included:

- Life style: information on smoking and alcohol/drugs use, diet, housing conditions, hobbies and occupational exposure
- Socio-economic status needs to be documented (using the ISCED education levels)

- Residential history: number of years living in the country need to be reported
- Geographical coverage: urban/sub-urban/rural
- Sampling time period needs to be reported i.e. no seasonal restrictions are set.

3.1.4.3 Sampling frame

The sampling frame is the list of the target population units from which the sample is drawn. The frame should be defined in a way to achieve a representative population composition of that subgroup. As such the sampling frame depends a lot on the chosen target population, e.g. general population by population registers, school children by schools, working population by companies, newborn-mother pairs by maternities/hospitals. The way of recruiting the participants is not prescribed within HBM4EU. However, a good sampling frame model for selection of individuals is the stratified clustered multi-stage design. Via this design, geographical areas (stratification) are selected within a country. Within each of the geographical areas, primary sampling units (PSU: schools, work registries, general practitioners) are selected randomly, however that can be done in a way that there is an increased selection chance proportional to the number of individuals in these PSU. Furthermore, individuals are selected randomly within the PSU.

3.1.5 Phase 0: Recruitment and Fieldwork I

After decisions on the target population and the sampling frame have been taken, decisions on the general recruitment and the individual contact to the potential participants are up next. An important aspect within the issue of recruitment of participants is the communication: Who shall be contacted in which way? Suitable communication is key when aiming to ensure a successful contact to the participant and to reach acceptable participation rates (Exley et al. 2015).

Table 5 provided an overview of possible sampling frames informing about where the address of the potential participant can be obtained. To get the addresses, population registers, clinics or doctors or employers or the head of institutions (schools, kindergartens) or education authorities have to be approached formally with an official letter explaining the study and the aim of the approach.

General ideas that have to be considered for decisions on the timing and duration of the study are shown in Table 6.

Table 9 provides an overview of recommendations for the general communication with different groups. Specific templates for most of the recommended documents will be provided by Task 7.5 in deliverable D7.4 or D7.7.

Table 9: General communication

Groups	Recommendations for communication measures/material
Adults general population, occupational groups, vulnerable groups	Implement communication strategy presenting the specific study and the general HBM4EU framework, spread it via media + internet + the specific centres involving target participants. Provide information leaflets and hand-outs describing aims, structure and detailed participation arrangements of the survey → sent by mail or other approaches as appropriate, for occupational groups: make it available at the workplaces, workers' clubs and recreational facilities, trade unions offices), for patients make it available at the hospital facilities /outpatient clinics /community centres
General information	Press releases/videos (in national and regional newspapers and other media including Internet website), flyers, newsletters, posters, banners, study information leaflets at general health practitioners/health centres, for occupational groups: at workers offices and clubs, trade union offices
Individual information	Invitation letter, participant information sheet, consent form

Groups	Recommendations for communication measures/material
Children /adolescents (different age groups)	Provide preparatory meetings with school administrators, teachers/educators, and children's parents, before and during recruitment phases, with distribution of information leaflets and hand-outs describing aims, structure and detailed participation arrangements of the survey and the general HBM4EU framework
General information	Flyers, posters, study information leaflets at kindergarten/schools, parent's residence, articles in local newspapers and TVs, newsletters
Individual information	Invitation and information material sent to parents or/and to teachers; consent form from parents and also from children starting at age 10-12

Decisions on the fieldwork of the study and its timing also include decisions on communication and vice versa therefore already at this planning stage implications of the communication aspects are important to know (Exley et al. 2015, Fiddicke et al. 2015). In Table 10 some general recommendations on method and frequency to approach participants are given (Bates et al. 2005, Keune et al. 2008, Fiddicke et al. 2015, Mindell et al. 2015).

Table 10: Method and frequency to approach participants

Groups	General recommendations I
Adults (general population)	**Individual invitation letter** - Personalized invitation at least 3-4 weeks before the examination date - Invitation to include the date of the proposed appointment (possibly including a return card to book the appointment, or to modify the proposed appointment) - Reminder of the appointment (e.g. with text message/SMS) - Length of questionnaire influence (negatively) the participation rate depending on the type of questionnaire application (before or during the examination, web-based and in advance, etc.) In case of no reply by study participants within 3 weeks, follow-up with phone calls and/or a second reminder letter offering a new appointment time (max. 6 additional contact attempts)
Vulnerable population (pregnant, new born, senior, etc.)	The invitation should be highly personalized and endorsed (or sent) by a confident person (GP, Paediatrician, Gynaecologist, Midwife Hospital/Clinic, Health Centre, Maternity/Lactarium). Home visit instead of meeting at the survey office should be considered.
Occupational population (partly)	Similar indications than for the adult population. Preliminary agreement about appointment time and survey approach methods with the participant employer and/or with the employee organization, at least one month before the survey date.
Children /adolescents (different age groups)	Similar indications than for the adult population, but request for participation and survey information should be addressed to both children/adolescents and their parents. Preliminary agreement about appointment time and survey methods with the school administrators and teachers/educators, as well as participant parents, at least one month before the survey date.

3.1.6 Phase 0: Fieldwork II

In Phase 0, decisions to be taken related to the personal involvement of participants can be derived from following five main questions:

- **What** does the study ask from the participants?

This addresses the question on **which instruments shall be applied** to the participants. It is of importance here to clarify and settle every aspect that is asked from the participants, be it samples taken from them or their home or their time. Ethics aspects must be included in the considerations.

Some aspects can be invasive (depending on the **matrix**, the volume and amount of samples to be taken), others can present a burden by being time consuming or touching their privacy (dust samples).

Most of the time spent would most likely be on the **questionnaire**, self-administered or through face-to-face-interviews, needed to collect information on possible exposure pathways. The questionnaire mainly covers topics of living conditions and habits/lifestyle, health, nutrition, socio-demographics, occupation and should have additional modules: substance specific, non-responder and satisfaction questionnaires. The scientific curiosity has to be balanced with the time burden questions put on participants.

Additionally, **medical parameters** (weight, height, blood pressure, etc.) as well as markers of physical condition (ECG, lung function, etc.) might need to be examined directly from the participants. And some studies add **additional sampling** like dust, indoor air or drinking water samples. Again, this puts time and inconvenient burdens on the participants which have to be considered as they may influence the participation rate, too.

All samples taken will probably need to be processed already at the sampling location, this also needs to be considered.

- **How** long will the participants be occupied with survey demands?

This question pertains to the whole duration of fieldwork. It involves all aspects addressed above like physical examination, questionnaire (self-administered or interview) but additionally time spent to stay in contact with the study organisers. This also includes if the participant shall be involved just one time or several times within the study (or a follow up).

- **When** will the survey be conducted and the participants involved?

The period of time for the whole fieldwork phase should be settled beforehand. The decision should be preceded by considerations of target group and their respective occupation (e.g. a study planned to involve school children mainly at the schools should not take place during holidays).

- **Where**: At which site will the participants meet the study, what is the **place of direct contact** to the participants?

Commonly used options to encounter the study field staff are the home of the participants or a place of productive hours (work place, school, kindergarten). Official examination centres can be organized in schools, clinics, town halls, etc. or mobile labs can be the site to meet the participant. It is advisable to offer alternative possibilities to the participants if appropriate for the study instruments. If, e. g. additional samples from the home of the participants (like indoor air or drinking water) are part of the study or the questions of the questionnaire need expert judgment on living conditions a home visit is recommended.

- **What** will the participants receive for their burdens/contribution?

In order to keep up participation rates, it is important to ensure the participant is aware of their advantage when taking part in the study therefore they can be offered incentives**. Incentives** can be information on study and general or individual-level results as well as financial and in-kind rewards (reimbursement for travel costs and/or for spending time and samples) or small gifts and certificates for participation (see Table 11). The feeling of ‘personal involvement’ with the study by participants can be increased by inviting them to provide input and suggest research questions or even participate in the research.

More specifically, various forms of incentivizing study participants exist, and the selection has to be individually tailored to the specific study population. Depending on the expected barrier to enrolment/participation, such incentives could comprise organizational aspects including additional

information (e.g., home visits, direct mailings, etc. see Table 11 for additional examples) or support in recruitment through reduction of administrative burden or similar measures. It is advisable to think through the enrolment process and participation to identify potential barriers upfront, and think about ways how these could be addressed. However, the process of deciding which incentives, especially as they regard organizational aspects of the study, to apply, should remain flexible throughout the active phase and should be prepared to address any newly emerging barriers or needs as they evolve.

In addition to organisational incentives, monetary and non-monetary incentives should be considered and chosen, if there is an anticipation that they could help increase participation. Such incentives typically comprise either reimbursements of expenses that participants incur due to their study participation (e.g., travel cost), or small gifts that can be tailored to the specific target population (e.g., smaller wearables for younger participants, gift cards for adult participants, etc.). Here, the expertise and insight of peers or stakeholders from the respective population can be drawn upon.

With regard to incentives, decisions also have to take ethics permissions into account. Incentives can be provided (partly) before and after involvement in the study. Small (monetary) incentives provided with the first invitation can increase the participation rate. Which incentives are to be expected when participation is finished shall be addressed in the first information.

Table 11: Types of common incentives

Type of incentive	Incentives and other measures to increase the participation rate and their impact
Information (see also Phase 1+3)	Raise interest and awareness, offer information on study and general results, direct mailing, home visits, provide individual results and advice
Support recruitment	Choose suitable recruitment places (schools, work)
	Reduce the administrative burden of address holder (e. g. GPs) to encourage them to recruit participants
	Link HBM study to on-going routine surveys etc.
(Non-)Monetary	Reimburse participants for travel costs and/or for spending time and samples
	Offer cash payments or in kind payments (small gifts) or certificates for taking part
Staff as promotor	Sustain staff commitment to the research through continuing training (see also Phase 4)
Evaluation (see also Phase 4)	Identify barriers to participation, non-responder questionnaires, comparison to target population
	Administer a reduced assessment battery

More ideas on Fieldwork II can also be found in Phase 4 (Section 3.5.2).

3.1.7 Phase 0: Questionnaires

As described under Chapter 3.1.7 Phase 0: Questionnaires are a main instrument of HBM-Studies. They help to elucidate exposure pathways and provide information on specifics of sample taking. In the Planning Phase it has to be decided how much time shall be spent for answering the questionnaire (remind the participant burden!), in which way a main (basic) questionnaire shall be applied, e.g. in a face-to-face performance or self-administered (paper and pencil, Computer Assisted Investigation CAPI, or online). Also the dimension of a non-responder questionnaire has already be laid down for the ethics authority. Each applied instrument should be accompanied by a tailored questionnaire, e.g. for the urine sample it is important to know when the sample was taken,

when and what the last meals were, etc. Therefore the sampling questionnaire is necessary, it is a written record of every event that occurs during sampling and all sample-related parameters (date and time of collection, volume, length, colour, problems encountered, etc.) or any particular information necessary for the interpretation of the results and it is related to the moment of the sample collection. If a new questionnaire is going to be developed decisions on the way of validating it have to be made and small pilot studies have to be taken into account. In the frame of HBM4EU Task 7.3 takes the responsibility to develop several questionnaires e.g. a basic questionnaire to collect information on socio-demographic characteristics, lifestyle, specific questionnaires for first prioritised substances, sample specific questionnaires and satisfaction questionnaire for the first prioritised substances. The questionnaires will be provided in deliverable D7.3 Annex 2.1.

3.2 Phase 1: Preparatory Phase

After decisions have been taken in Phase 0, the Preparatory Phase (Phase 1) begins, i.e. all parameters which have been decided upon have to be prepared such enabling the start of the fieldwork. Most preparation is necessary on documents be it for communication issues, for fieldwork, for quality issues (SOPs) or for data management and the request for permissions. This Preparatory Phase can also take some months.

At the latest at the beginning of the Preparatory Phase decisions on the **responsibilities** for different parts and issues of the study conduct have to be fixed. Decisions on conducting a regional or national study mostly involve different organizational bodies. The **study owner**, as the body responsible for (financing) the study (i.e. a country, federal ministry or research institution), usually delegates the operational tasks to an **administrative body** (i.e. a federal, regional or local agency, or research institute). This administrative body, or in case a delegation is not necessary, the study owner directly, is responsible for the proper implementation of the study (directly or using subcontracts).

Implementing a study includes the organization and conduct of the study. It is therefore connected to the establishment of a **Survey Office** which functions as the central unit for conducting fieldwork and is responsible for managing recruitment and sampling of participants i.e. is responsible for general aspects, organizational background with long-term preparation. The Survey Office is mostly supported by **field staff** that takes charge of aspects happening at the sampling location which can be organized on short notice, i.e. is responsible for the direct interaction with the participants during the fieldwork. Due to this separation of duties, it is the duty of the Survey Office to take care of all issues of the Preparatory Phase.

Important tasks for the Survey Office in Phase 1 if a new study is planned are listed below. Additions for aligned studies may be necessary (see in brackets). Table 1 already provided an overview.

- Preparing/start preparing the Study Protocol, Fieldwork Manual and SOPs (aligned studies may need extensions)
- Developing and applying a concept for data management and authorization by data protection agencies (aligned studies may need extensions).
- Applying for authorization of the study by ethics committees (aligned studies may need extensions).
- Creating a database for the contact details, and a separate one for the questionnaire data and analytical results (aligned studies may need extensions).
- Preparing a protocol sheet to track the recruitment procedure (first personal contact until appointment is fixed).

- Ensuring the availability of all communication material, non-monetary incentives, a reception sheet for monetary incentives and all **questionnaires** in the main country language(s). Written materials should be translated into languages country inhabitants and main immigrant groups usually speak and be available in printed form as well as electronically (aligned studies may need extensions).
- New developed questionnaires for the first prioritised substances for HBM4EU have been developed by Task 7.3 and are provided in deliverable D7.3. Testing the translated questionnaires is in the responsibility of the Survey Office of each country (10 to 15 test interviews with volunteers need to be performed) (may also be necessary for aligned studies).

Following aspects have to be taken care of for the **biological samples /analytics**:

- Part of the communication material are also documents providing advice for the participants for storage and handling of the samples the participants have to take, these have to be prepared.
- Either contact a lab of the own institution or prepare documents to tender laboratories (may also be necessary for aligned studies). The intended limit of quantification of the selected biomarkers has to be taken into account.
- For HBM4EU project the samples have to be analysed in laboratories that achieved successful results in the HBM4EU ICI/EQUAS scheme for the corresponding biomarker.
- Sample traceability: Guarantee the unambiguous identification of the samples, aliquots and related documents. Check the quality of the labels employed and ensure that the ID code remains legible irrespective of the conditions (temperature, humidity, etc.) and that the label remain stuck to the tube, vessel or document (should already be tested for aligned studies).
- Prepare a sample reception protocol to be filled in by involved labs, necessary to control the integrity of the packaging and the conditions of the sample tubes and vessels
- Database of aliquots: Create a database including the sample ID code, aliquot ID code, sampling date, freezing date, type of sample, aliquots remaining after analysis, location in the bio bank, etc. (should already be present for aligned studies)

Time necessary for preparation shall not be underestimated as all parts of a study (data management, communication, fieldwork including recruitment and sampling, analytics) are complex issues –sometimes just realized while working on the details.

The Study Protocol provided here focuses on recruitment, sampling and fieldwork but gives short information on the other issues necessary for a proper study conduct. Within the HBM4EU programme this preparatory work is shared. Several working groups are involved as indicated in Table 12: e.g. Task 7.3 will prepare the questionnaires for upcoming studies, including a basic questionnaire, a sampling questionnaire as well as questionnaires to evaluate satisfaction and non-responders. Communication material as non-monetary incentives will be provided by Task 7.5. For Ethics and Data Protection matters, Task 1.5 will be involved and Data Management is handled by Work Package 10, analytics by WP9.

Table 12: Tasks of Phase 1 and respective main documents

Tasks of Phase 1	Respective main documents
Prepare a Study Protocol, start Fieldwork Manual	Deliverable 7.3 (Annex 1 and 2)
Prepare (and test) questionnaires & Interviewer Manual	Deliverable 7.3 (Annex 2.1)
Prepare analytics	Deliverable 7.3 (Task 7.3)
Prepare data management	Deliverable 10.1 (Task 10.1)
Prepare communication material	Deliverable 7.4 (Task 7.5)
Apply for authorisation (Ethics & data protection)	Deliverable 1.5 (Task 1.5)

3.3 Phase 2: Concretisation Phase

After careful planning in Phase 0 and preparation in Phase 1, Phase 2 comprises the concretisation of the work ahead, tasks are started to be turned into practice, e.g. material is bought or labs contracted. At this point, all prerequisites for the study, like ethics authorization and data protection issues are solved.

Table 1 already addressed the matters most important in this phase. Table 13 provides a more detailed overview. Responsible for the implementation of these tasks is the Survey Office.

Table 13: Overview of the tasks of the Concretisation Phase and needs for application

Concretisation phase	Apply for
Finalisation of the Fieldwork Manual with all SOP and questionnaires	New study / aligned study
Engage qualified interviewers/ fieldwork staff	New study / aligned study?
Organise and perform the training of the interviewers /fieldwork staff	New study / aligned study?
Buy material for the sampling of the matrix to be collected (sample vessels, aliquot tubes) and material for the field staff (laboratory equipment, office and dispatch material). If necessary, prepare the material for the sampling (clean with acid solution, label it, etc.). Also material for the transport of the samples to the laboratory or biobank have to be taken into account.	New study / aligned study
Fix relation to intended laboratories, sign contracts. Define the date and delivery format for the results: type of file, units, report about the internal quality controls applied, etc.	New study / aligned study?
Organise the incentives which have been selected for the participants (books, bags, etc. with study logo) and a reception sheet for monetary incentives	New study / aligned study?
Provide packing lists and prepared material for the field staff	New study / aligned study
Decision on exact start date and duration of the fieldwork	New study / aligned study
Schedule the visit of the sampling locations (e.g. cities) (provide a route plan)	New study / aligned study?

3.3.1 Phase 2: Fieldwork Manual and field staff

In order to ensure successful fieldwork, the finalisation of a detailed **Fieldwork Manual** has to be elaborated, the preparation of which already started in the Preparation Phase. A well-elaborated Fieldwork Manual is of the essence to cover the entire process of the fieldwork and answer possible questions. It can also be called operational manual and contains written information on all procedures, instructions and guidance for use by the personnel in the execution of their duties and blue prints for needed documents which were prepared in the Preparation Phase (see separate document ‘Fieldwork Manual’, Deliverable 7.3 Annex 2).

A careful selection process for the **field staff** has to be employed as a matter of quality assurance; individuals with experience in similar studies can be an asset. The field staff, especially interviewers for face-to-face interviews, are the direct contact persons for the participants, they “create” the quality of the collected data and samples. The number of persons engaged is in relation to the sampling points and number of households in that sampling point. Medical education is necessary if blood samples shall be taken. The field staff should be able to substitute each other in case of unforeseen absence.

Before the start of the study, the field staff needs to be trained. A training workshop has proven to be necessary. This workshop should not only explain details of the work flow (how to plan and conduct the interview, how to take samples, sample aliquoting, transport, sample reception, filling out all documents involved in the sampling procedure. etc.) but should also provide an overview on the study itself, its background, the background of the questions and specific topics. It is important that the entire field staff is given the same background and instructed in similar fashion (e.g. to read each question literally) to avoid bias (also see Deliverable 7.3 Annex 2.2.2 SOP 2: Quality Assurance for Recruitment and Fieldwork).

To ensure quality and comparability, a test run with voluntary participants should be considered. Interviewers should also answer the entire questionnaires and do the sampling themselves.

In case there are indications the conducted fieldwork does not comply with the required processes and documented Standard Operating Procedures, it might become necessary to organize a refresher course for the field staff.

Last but not least, Phase 2 also includes the creation of a detailed fieldwork schedule with start date, end date and route plans for the field staff.

3.3.2 Phase 2: Biological samples / Analytics

Organisation and control during the fieldwork: If it has been decided that the samples of the participants will be handled directly in the field, it might be necessary to have a minimum laboratory equipment, e.g. refrigerator, centrifuge, etc. and appropriate facilities to avoid the contamination of the samples. These devices have to be ordered in the Concretisation Phase. Also conditions for the conservation and transport of the samples during fieldwork have to be checked in advance to ensure its optimal conservation in order to avoid the loss of samples in the fieldwork. Furthermore, the packaging must fulfil the regulations (local and general) concerning the shipping of biological material. Material has to be ordered. If the transport will be done by couriers, the coverage of its service needs to be checked in advance to prevent loss of samples.

Pertaining to the organisation of the sampling and aliquoting a sample reception protocol has to be distributed. This protocol shall be applied during the reception of the samples arriving to the laboratory. This procedure should include the checking of different items to control the integrity of the packaging and the conditions of the sample tubes and vessels to identify any problem that can pose a risk for the quality of the sample. Any problem encountered should be recorded in a specific document (the sample reception registry). Samples regularly need to be checked against criteria for acceptance/rejection of samples when arriving to the laboratory.

One important part of HBM-studies is the analysis of the collected biological samples. In the Concretisation Phase the relation to the labs which shall analyse the samples has to be fixed, i.e. necessary tender processes finalised and contracts signed. It is also advisable to fix the date for reporting the results and clarify the format of the deliverable, e.g., the units, the format of electronic file, if the report will inform about the internal quality controls applied for the laboratory during the analysis, what happens if the results are not available at the delivery date, etc.

3.3.3 Phase 2: Incentives

A decision about which incentives to apply initially, will have been made at this point and they will be ready for use. However, the process of deciding which additional incentives, especially if they regard organizational aspects of the study, to apply, should remain flexible throughout the active phase and should be prepared to address any newly emerging barriers or needs as they evolve. If a decision towards incentives, e.g. monetary (vouchers) or small gifts, has been taken, these will have to be organized or bought in the Concretisation Phase. In case money is paid (e.g. reimbursement for time efforts and travel costs) receipt forms must be prepared to document payment. Frequently, these also involve the assessment of participant-sensitive information (e.g.,

social security number) which could pose a barrier that ought to be considered when preparing such incentives.

3.4 Phase 3: Starting Phase

After the preparation phase has been finished, Phase 3, the Starting Phase, begins. This is some weeks before the fieldwork in one sampling location starts and pertains all that is necessary to be able to visit participants or welcome them in an examination centre to take part in the study.

The Starting Phase includes several tasks for the Survey Office that mostly need to be done for new studies only (assuming that studies to be aligned have already begun).

3.4.1 Recruitment

The most important part of a study is the recruitment of participants which starts with organising and acquisition of participant addresses. Depending on the target population and the sampling frame that have been decided about in Phase 0 the addresses of potential participants can be drawn from various sources. A first step is to organise the addresses of potential participants e.g. from population registries, from patient files, or schools. This can be done some weeks in advance but it has to be paid attention to the possibility of changing addresses which increases with the timely distance between searching for addresses and sending individual invitations.

In order to perform a study that is representative of the target population, a random sample of that population should be drawn. If it is not possible to approach population registers other kind of registers could be approached. Telephone directories used to provide a complete picture of adults of a specific region and in some countries they still do.

Address holders (registries or institutions) have to be approached or in case this is not possible potential participants can be approached directly (like pregnant mothers in maternities). In any case emphasis should be put on a random sample as representative of the target population as possible (details see Deliverable 7.3 Annex 2.2.1 SOP 1: Selection of Participants and Recruitment). An overview is provided in Table 14.

Table 14: Phase 3 (Starting Phase): Obtaining addresses of potential participants

Target population	**Sampling frame** already decided in Phase 0	**Address of first contact** (whom to contact in Phase 3)
General population separated for gender/age	Population register (country, regional)	Holder of list: contacted via formal letter. Participants of ongoing studies: Study personnel (contacted via formal letter)
Vulnerable population (pregnant, newborns, seniors etc.)	Patient files, clinics, doctors	Confidant/ Head of institution (contacted via formal letter or personal visit)
Selected occupational population	Employment records, branch organisations	Head of organisation (contacted via formal letter or personal visit)
Children, adolescents (different age groups)	Kindergartens/day care centres, or their groups	Head of institution (sometimes at first the education authority have to be contacted) (contacted via formal letter or personal visit)
	Schools, vocational schools, or classes	

After an address list of potential participants is obtained the completeness of the list has to be checked and safeguarded to be able to perform the selection procedure according to statistical routines taking care of the proper representativeness of the study.

The addresses are necessary in order to establish a first contact with potential participants via letter, call or personal visit.

3.4.2 Filling databases

For new studies, the databases set up in Phase 2 now have to be filled with these addresses of the potential participants and a study-specific ID-number for each potential participant has to be added, which serves for pseudonymisation of results. During this process and from here on out, data protection always has to be ensured.

3.4.3 Prepare fieldwork at sampling locations

Besides being prepared to contact participants, in the Starting Phase also preparations at the first sampling location (i.e. the region or city where the study will take place) are included; these have to be repeated in each sampling location participating in the study. E.g., if appropriate, rooms have to be acquired that serve as examination centres at the sampling locations as well as rooms for the field staff. This might also be necessary to do for aligned studies, depending on the initial study's characteristics. Examination centres can be schools, town halls, rooms in clinics or other premises. Most important is that they can be reached easily, preferably with public transport and that they serve the needs for the study (waiting room or reception, room for interviews, room for exercises, sanitary facilities, etc.).

3.4.4 Inform general public

At the same time, information of the general public about the study at the sampling location has to take place. This serves to raise awareness for increasing the participation rates (see Phase 0, Section 3.1.5, Table 9).

3.4.5 Inform the labs

Laboratories hired to analyse the biological samples have to be informed about the upcoming start of the fieldwork to prepare them to be ready to start the moment the first samples will reach them.

3.5 Phase 4: Fieldwork

As indicated in Table 1, Phase 4, the Fieldwork Phase, can in turn be split up into two phases. They differ in their way of involving the participants.

3.5.1 Phase 4: Fieldwork I

Fieldwork I revolves around the first contact with individual participants, their invitation and clarification of their inclusion, the fixing of an appointment for their personal involvement, as well as the provision of material to collect samples with.

Fieldwork I can also be described as recruitment on the individual level (whereas the word "recruitment" also includes recruitment on the general population level and therefore includes the contact to address holders etc. as mentioned above in Phase 3). In this Phase 4, Fieldwork I, the duties of the Survey Office include the preparation and sending of individualized communication material like a personal invitation including informed consent to potential participants.

The Survey Office will receive participants' answers and is in charge of the recruitment interview where it is checked whether inclusion criteria are met or the potential participant has to be excluded. Included participants will be send further material necessary for the study, e.g. material to collect samples (e.g. urine vessels) or self-administered questionnaires. Further duties are described in Table 15.

Table 15: Duties of the Survey Office during Fieldwork I

Fieldwork phase I	Apply for
Prepare and send individualized communication material including informed consent and a kind of reply card to potential participants	New study / aligned study?
Install a help-desk phone number for the participants	New study
Perform recruitment interview and check whether inclusion criteria are met or not	New study / aligned study?
Use the protocol sheet to track the recruitment procedure from the first personal contact until an appointment for individual participation has been fixed *(if appropriate)*	New study
Perform the non-responder interview via telephone if a potential participant refuses to participate	New study
Provide and fix appointments for the participation in interview/examination/sampling *(if appropriate)*	New study
Send material to collect samples (e. g. urine vessels) or self-administered questionnaires to the included participants *(if appropriate)* including storage and handling advice for the participants	New study / aligned study?
Provide the field staff with the participant addresses *(if appropriate)*	New study
Keep a thorough documentation of each decision, action, accomplishment and comments received from participants and staff (also in Fieldwork phase II)	New study / aligned study

In case the Survey Office is not able to reach all selected participants to ask them for their participation it is the duty of the field staff to contact potential participants when they arrive at the sampling location because for statistical reasons it is necessary to try very hard to reach each random selected participant (see Fieldwork II below).

3.5.2 Phase 4: Fieldwork II

Fieldwork II focuses on the involvement of the participants in the survey, mainly done by the field staff. It includes the interview or the self-administered questionnaire, the examination, taking of samples, provision of incentives and notification about the results. All preparations need to be finished: the core element of the study is starting.

3.5.2.1 Individual recruitment procedure

Figure 1 provides an overview of the recruitment procedure on the individual level. Starting from the participant address and the first official invitation, the figure shows how to continue in case of agreement, disagreement or no response from the participant up to the point in time when an appointment with a potential participant is fixed – turning the potential participant into an actual participant.

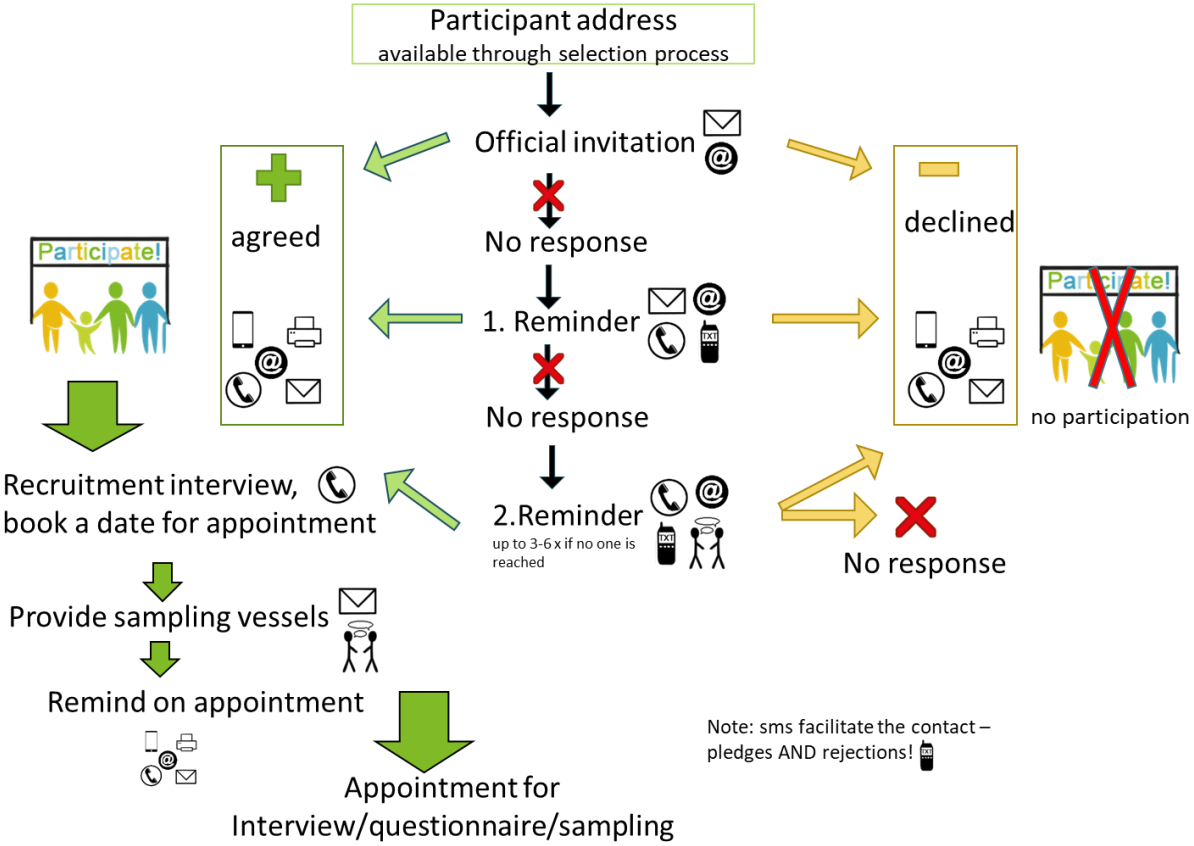

Figure 1: An overview and recommendations for individualized communication

Lessons learnt from already conducted studies show that the first individualized invitation for the study should be send to the potential participants about three to four weeks in advance to the expected participation of the participant. This may lead to the 3-week-plan shown in Table 16.

Table 16: Example for approach to general population, starting 3 weeks prior to begin of study

Days	
1	Send official personalized invitation (including the date for proposed appointment and a reply card)
2-9	Waiting for response
10	1. Reminder
11-15	Waiting for response
16	2. Reminder
17-20	More reminders if necessary (personal visit by the field staff)
21	Envisaged participation

Note: Text messages facilitate the contact, for pledges **and rejections!*

Fieldwork II includes mainly the **duties of the field staff**, i.e. involving participants more directly in the study. Figure 2 shows some alternatives to do so (there detailed planning and preparation has already been done in Phases 0-3).

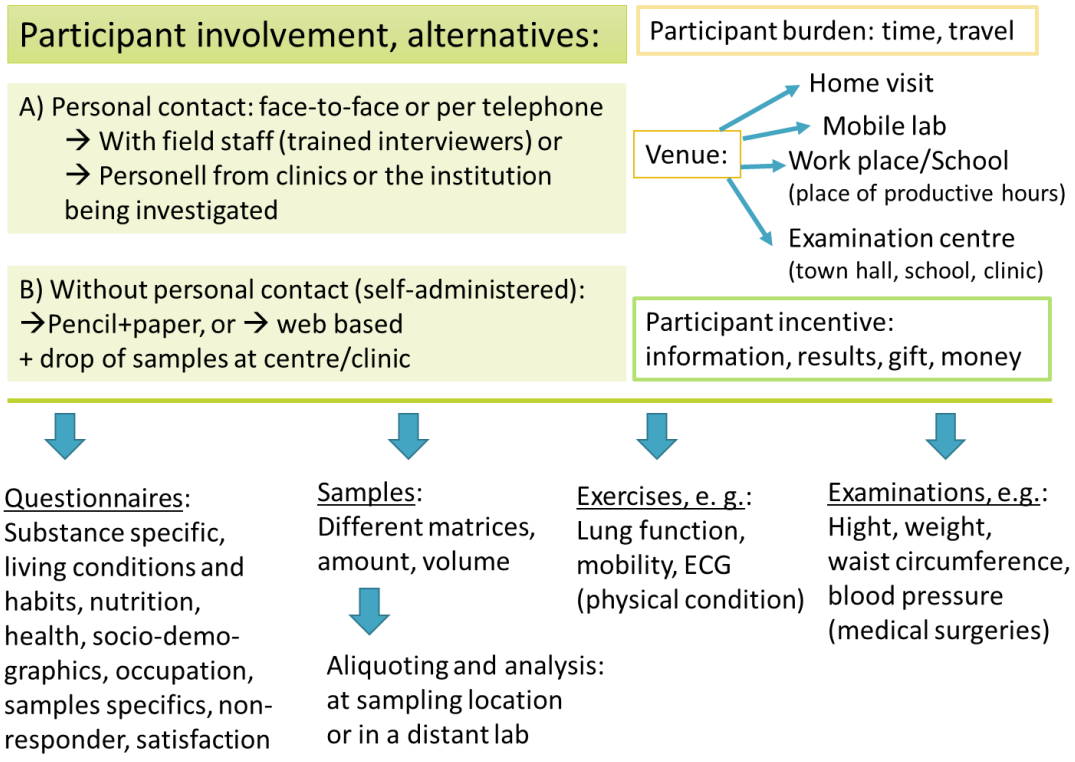

Figure 2: Alternatives for participant involvement

Participants can be involved through **personal contact** with the field staff. Maybe a first personal face-to-face contact can be necessary to ensure participation, particularly if other measures (letters, phone contacts from the survey office) did not succeed to enrol the potential participants (this first visit is part of Fieldwork I). Personal visits of the field staff at the home of the potential

participants (if not reached by phone) is the last possibility to ask potential participants for their participation.

An actual first face-to-face contact can be the guided interview either through trained interviewers or personnel from the institution that is involved in the study (e.g. personnel from clinics) with the traditional pen and paper or a Computer-Assisted-Personal-Interview (CAPI).

Participant involvement can also be achieved without personal face-to-face contact. This includes a self-administered questionnaire, e.g. sent by mail (pen and paper) but also web-based applications. Self-administered participant involvement will include some form of dropping of samples at a centre or clinic or a transport by mail while it is most important to provide distinct storage and handling advice for the participants.

Whether the **venue** of the direct involvement is at home during a home visit, at a place of productive hours (work place or kindergarten) or at an examination centre (town hall, school, clinic), or, less common, in a mobile lab, the participants will always be burdened in some form (time spent and travel effort). Therefore it is advisable to offer alternative possibilities, e.g. participants can choose to be visited at home or visit an examination centre near to their home to take part in the study.

In order to compensate for their burden, participants can receive **incentives**. These incentives (to be decided already in Phase 0) are often information, personal results or money, but can also be goodies (e.g. toys for children). For an overview, see Table 11. Use of incentives should be discussed and agreed upon by a (national) ethics committee. It has been shown that small (monetary) incentives provided before the start (together with the invitation) increase the participation rate.

Depending on the study design, the **direct involvement of participants** requires to provide samples, partake in exercises or examinations and complete questionnaires. For the Survey Office or field staff this often means several study-specific details have to be considered when planning the venue of the participant involvement. **Samples** can include different matrices, can vary in amount or volume and need handling (aliquoting, transport and analysis), either collected by trained staff or by the participants themselves. If exercises to determine the physical condition are necessary, e.g. to test lung function, mobility or to record an ECG, the required measuring instruments have to be available (ordered already in Phase 2). Other examinations, e.g. for height, weight, waist circumference and blood pressure, might be possible to perform in a different/second venue and might need different skilled field staff.

Questionnaires, self-administered or guided by an interviewer, are an essential part of many studies. While there are several options when bringing a participant into contact with a questionnaire (self-administered or completed during a home visit or phone interview), it usually takes quite some time to fill out and is hence likely to heighten the participant burden. Questionnaires can be substance or sample specific, cover living conditions and habits, nutrition, health, socio-demographics, occupation or participant-impression related, like non-responder questionnaires and satisfaction questionnaires.

3.5.2.2 Preparations for participant involvement

Fieldwork II, the direct involvement of the participants requires careful planning to ensure **proper study conduct**. This planning concerns all phases of the involvement. The field staff is required to take care of several matters. The following steps are mandatory for new studies with personal contact to the participants and facultative for aligned studies.

- **Prior to the visit** of the sampling location, the field staff (interviewer) needs to stock up the necessary material for the visit of the sampling location (procured by the Survey Office in Phase 2), to be prepared to stock up the materials before each single participant visit.
  The field staff also receives from the Survey Office addresses of the participants for the sample location to be visited. In case a stay overnight is necessary, an accommodation should be rented (already in Phase 3).
- **Upon arrival at the sampling location**, the accommodation or examination centre has to be furnished with study equipment and devices.
  At this point in time, the field staff also tries to contact one last time potential participants that have not been reached so far by the Survey Office.
- **The day before visiting the participants** in their home or at the examination centre, the equipment necessary for the upcoming visit (such as interviewer identity card, papers, laptop, additional sampling vessels, incentives etc.) has to undergo an integrity check. Maintenance and record of study devices (e.g. refrigerator for short-term storage, pipettes for aliquoting) should be performed every day.
- **During the visit**, special care has to be taken if the participant involvement takes place in the participants' homes. Respect for the residents and close observation of household etiquette is strongly recommended to avoid negative effects on participation rates.
  Ahead of any other actions taken, the interviewer checks and accepts the declaration of informed consent from the participant. Afterwards, the questionnaire can be filled out, measurements and samples taken. There should always be a certain flexibility in carrying out these tasks to adapt to the most convenient order for the participant.
  The visit needs to be well documented with details concerning duration, completion, handovers and consent.
- **After the visit to the participant**, be it in his or her home or at an examination centre, the samples need to be processed. Transport or shipping to the accommodation or Survey Office or even directly to the laboratory needs to be conducted according to shipping protocols.
  An additional visit at the next few days should be offered to the participant if not all parts of the study were completed at the first visit.
- **Once all visits at a sampling location have been completed**, location reports (numbers and potential issues) are to be sent to the Survey Office. In case samples have not yet been shipped, they should be sent out to the Survey Office or directly to the laboratories at this point.

3.5.3 Phase 4: Biological samples / Analytics

During Fieldwork II biological samples are received from the participants. Either they have to be prepared for further processing (aliquoting) or for shipment to the analysing laboratories which have been (sub-) contracted. Shipment has to follow Standard Operating Procedures (see also Deliverable 7.2 Annex 1 SOP: Sample Exchange on a pan-European level to be used in the HBM4EU initiative) to warrant high quality of samples.

3.5.4 Phase 4: Questionnaires

Application of questionnaires is a duty of Phase 4. As pointed out on the preceding page and under Phase 0, there are different ways to involve participants with questionnaires. In most studies different kind of questionnaires are applied in different ways, e.g. a face-to-face interview for the large basic questionnaire which covers nearly all exposure pathways and also asks general questions on socio-economic variables. Sample specific questionnaires are often self-administered (and checked by an interviewer when he accepts the samples). Health questionnaires sometimes are send sent by mail or via an online tool for self-administered use. To cover exposure pathways of the first prioritized substances in the frame of HBM4EU a set of questionnaires is developed by Task 7.3. The basic questionnaire is attached to the deliverable D 7.3, there also information on

necessary translation and an **Interviewer Manual** explaining the background of the questions can be found. If, for aligned studies, only some of the provided questions shall be used a logic sequence of the questions has to be warranted.

During **Fieldwork II** the **Survey Office** has several **duties** to fulfil, too.

These duties include the general supervision of the fieldwork (performed by interviewers or field staff, see also Deliverable 7.3 Annex 2.2.2 SOP 2: Quality Assurance for Recruitment and Fieldwork) and to provide help and advice if necessary, but also the conduct of internal quality control for fieldwork. Evaluation should be closely monitored by the Survey Office to check for signs of differential participation and to compare with the target population. It is further required to organize and conduct additional trainings for the field staff.

Additional training of field staff as well as a report covering experiences and lessons learnt to the responsible unit is required for both new studies and aligned studies.

Only for new studies (as in an ongoing study, data protection should already be included), the Survey Office needs to safeguard data protection when keeping the participants' addresses and it is also required to provide the data base filled with the questionnaire data (participants' answers) to the data management unit for **evaluation of study results**.

3.6 Subsequent steps

Shortly after the fieldwork is finished in one sampling location the procedure starts again for a next sampling location. In parallel, the laboratories can start analysing samples which is a prerequisite for reporting the results back to the participants (in which way this will be done had already to be described for the ethics authorization). But before results can be reported the data of the questionnaires and the samples has to be checked. After the fieldwork is completed in all sampling locations results of the different instruments have to be merged, checked and analysed with statistical software. Only then advice for the (general) public and politics can be provided.

4 Occupational Exposure

4.1 Integration of occupational exposure in general HBM-surveys

Information on occupational exposure may be obtained in general HBM-studies (or other studies such as cohort studies). In a study targeted towards the general population information on occupational title and type of work may be obtained through questionnaires or registers with information on occupation. Exposure assessment can be conducted either using a Job-exposure matrix (JEM) or through the biomonitoring sample (for exposures where this is possible). Table 17 lists advantages and disadvantages of integrating occupational aspects in general population studies or performing single studies on workers. An advantage of this approach is that information on a large number of potential confounders may be available and that information on exposure is obtained for individuals with a variety of occupations. A disadvantage is that it is often difficult to evaluate exposure based on job title (which will lead to exposure misclassification). Moreover a large sample size is needed to ensure a sufficient number of individuals in each occupation, in particular for more uncommon occupations.

Table 17: Integration of occupational aspects in surveys

Target population (study pop.)	Information on occupational exposures	Pros	Cons
General population study or large cohort	Add questions on occupation (and type of work) or link to register with information on occupation	Detailed information on potential confounders Information on exposure also in individuals with other occupations Larger exposure gradient when also general population with (nearly) zero exposure is included	Difficult to evaluate exposure based on job title (exposure misclassification) Risk of few individuals in each occupation
Employees in a specific occupation	Occupational setting with the defined exposure (direct measure of exposure possible)	Possibility to have more specific information on occupational exposure Larger number of individuals with the exposure of interest	No information on exposure in individuals with other occupations or the general population

4.2 Studies in occupational settings

An alternative approach to obtain information on occupational exposure is to target employees in a specific occupation and/or occupational setting. This may enable direct measure of individual exposure, which generally provides an accurate estimate of the actual situation, provided that the measurements are performed under normal working conditions and reliable methods and monitors are utilized in a suitable manner. An advantage with this approach is the possibility to have more specific information on occupational exposure and a larger number of individuals with the exposure of interest compared to HBM-studies of the general population. A disadvantage is that there is no information on exposure in individuals with other occupations or in the general population (see Table 17). The special requirements to the organisation of fieldwork in occupational settings are described in Table 18 (see also Table 1 for further Phases).

Table 18: Organisation of fieldwork in occupational settings

	Characteristics
0 – Planning Phase	**Decide on study design**, identify target population (i.e. occupational setting), choose participant selection procedure, recruitment procedures and contact procedures
	Define inclusion and exclusion criteria, and encouragement of participants
	Identify suitable occupational setting and/or workers (through trade organisations, unions, or registers with information on occupation)
	Decide on samples (which samples, selection of matrices/biomarkers, time for sampling, amount, type of test tubes etc.)
	Contact employer and possible also unions and/or trade organisation
	For Phases 1 to 4, please refer to Table 1.
Attention	**Other details to keep in mind when organising fieldwork in occupational settings:** Samples may be collected at the work place, in the home or at study centre depending on the type of biological samples (and additional data) collected and the work environment (it may not be possible to collect samples at work in all occupational settings). Coordination among those responsible for health-care at the industry/company/workplace should be considered.

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