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A Phased Approach for preparation and organization of human biomonitoring studies

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ABSTRACT

Background: Human biomonitoring (HBM) studies like other epidemiological studies are costly and time-consuming. They require the administration of questionnaires and collection of biological samples, putting substantial burden on the participants which may result in low participation rates. The growing importance of HBM studies in epidemiology, exposure assessment and risk assessment underline the importance of optimizing study planning, designing and implementation thus minimizing the above-mentioned difficulties.
Methods: Based on frameworks from survey design and fieldwork preparation of the European Joint Program HBM4EU, the German Environment Surveys and the COPHES/DEMOCOPHES twin projects combined with elements of project management strategies, a Phased Approach has been developed, introducing a step-by-step guideline for the development of epidemiological studies.
Results: The Phased Approach splits the process of developing a study into six phases: Phase 0 (Scoping and Planning): All aspects that are necessary to conduct a study are compiled and put on the agenda for decision-making. Phase 1 (Preparation and Testing): Instruments (e.g. questionnaires), materials (e.g. guidelines, information), and ethics and data management issues, needing thorough preparation and testing before a study can start. Phase 2 (Initiation): Organization and acquisition of necessary equipment and engaging and training personnel. Phase 3 (Implementation): All procedures that require temporal proximity to the start date of fieldwork, such as obtaining contact information of invitees. Phase 4 (Fieldwork and Analysis): Involvement of participants and chemical analysis of the collected samples. Phase 5 (Results and Evaluation): Final procedures leading to closure of the project, such as providing and communicating results.
Conclusions: The separation of the planning and conduct of human biomonitoring studies into different phases creates the basis for a structured procedure and facilitates a step-by-step approach reducing costs, warranting high participation rates and increasing quality of conduct. Emphasis is put on a comprehensive scoping phase ensuring high quality of the study design, which is indispensable for reliable results.

1. Introduction

Early epidemiological studies often focused on infectious diseases and death; modern epidemiology has a broader application. Environmental epidemiology studies can be classified into two categories: descriptive and analytical. Descriptive studies include case reports, ecological studies, and cluster studies while analytical studies are based on more detailed data from individuals that can be used to control for confounding, they are usually costlier and more labor-intensive.

Human biomonitoring (HBM) studies are environmental epidemiological studies and can be either descriptive or analytical in design. They include not only response to questionnaires, but also collection of biological samples such as urine or blood from the participants (Angerer et al., 2007). They aim at assessing the exposure levels of a population and establishing the exposure sources by applying statistical procedures on the laboratory results and the provided questionnaire responses

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(Kolossa-Gehring et al., 2012; National Research Council, 2006). Some studies additionally include the collection of environmental samples such as tap water or indoor air or dust samples from the homes of the participants (Kolossa-Gehring et al., 2012). Collecting materials and data has to follow a structured and quality assured procedure because every single step of the study has an impact on the overall quality of the conclusions (Calafat and Needham, 2009; Heffernan et al., 2020). Each one of these single steps needs to be decided upon because it can enhance or deteriorate the survey results and it needs (restricted) resources. Therefore, optimization of processes and resources is necessary. A so called "total survey design perspective" that considers all important aspects of study design can serve as orientation (Fowler, 2014).

Epidemiological studies that include participants in fieldwork are costly. What makes HBM studies even more costly and complex is the need for collecting biological matrices, transport and conservation, the chemical analyses, and related issues e.g. control of contamination and ethical considerations. As HBM gains strength, for example in the field of risk assessment (Angerer et al., 2007; Bates et al., 2005; Choi et al., 2015; Sobus et al., 2015) an increase in the numbers of HBM-studies is expected. At the same time, it has become more and more difficult to recruit volunteer participants for these time-consuming studies (Tolonen, 2015; Blair and Czaja, 2014).

HBM or other epidemiological studies require a wide variety of expertise such as project management, questionnaire development, data management, ethics, data protection, general and participant communication, logistics of materials and biological samples, chemical analysis, toxicology, statistics, personnel for the study conduct (interviewer, field staff, in some cases medical staff) etc. (Choi et al., 2014; Tolonen, 2016).

Successful conduct of a study relies on the development and execution of a well-organized research plan which includes the research question (incl. literature research), development of methods or instruments, study implementation as well as management and analysis of data and last but not least interaction and communication with participants (Weber and Cobaugh, 2008). Support for organizing and managing the resources for a defined project within a defined time period is provided by project management (Berkun, 2005). Project management includes establishing a multidisciplinary project team, defining, in balance with available financial resources, the project scope, developing a timeline, directing project activities, managing problems, and tracking the progress and ensuring quality in the whole process. For the development of a timeline the study needs to be broken down into steps or clusters of tasks, to which resources have to be allocated (Weber and Cobaugh, 2008). Applying these principles of project management to the planning of a study can lead to a better organized and effective study (Weber and Cobaugh, 2008).

Some support for the planning of epidemiological studies is provided by epidemiological associations when they explain which elements have to be generally considered or have to be described in a study protocol. According to the International Epidemiologic Association (IEA), "… the [study] *protocol is the cornerstone of any epidemiological research project*" (IEA 2007) which makes it the main instrument for implementing an epidemiological, or human biomonitoring, study. The study protocol - also called study plan, handbook, or book of operations – starts with a chapter about the purpose and the underlying hypotheses of the study. Following chapters refer to the study design, the study (target) population and the sampling frame to be applied and details about planned activities and analyses. Furthermore, administrative issues, ethical and legal considerations and possible problems and limitations are described (IEA 2007). There are standards of good scientific practice for study conduct available and should be followed by all epidemiologic research initiatives (IEA, 2007). Such standards have been published e.g. by the American Chemical Manufacturers Association (Cook, 1991) and by the German Society for Epidemiology (DGEpi) (DGEpi, 2008; Hoffmann et al., 2019). Whenever a country or institution is striving to perform an epidemiological study, e.g. a health and/or nutrition survey or a human biomonitoring survey including collecting biospecimen, it is well-advised to respect these guidelines.

However, while these standards provide useful guidelines, they do not inform about the roadmap for the planning of such studies which would be helpful considering the complexity of the studies and the different issues to be regarded. We propose here the Phased Approach which complements the existing literature on details of study design, fieldwork, ethics or data management (Ahrens and Pigeot, 2014) in providing a precise, practically and usefully structured, step-by-step approach for planning an epidemiological HBM-study in detail.

2. Methods

The Phased Approach was developed in the framework of the European Joint Program HBM4EU (HBM4EU, 2020). It is based on experiences of the German Environment Agency (UBA) which has conducted environmental surveys regularly since 1985 (Schulz et al., 2007). The experiences of the author and co-authors were already incorporated in the ESBIO project (Development of a coherent approach to human biomonitoring in Europe 2005–2007) (EU, 2013a) and the twin projects COPHES/DEMOCOPHES (EU 2013b; COPHES 2013), a European coordination action on HBM, and now in the Horizon 2020 project HBM4EU (HBM4EU, 2020).

In HBM4EU to some extent data from newly developed studies in different countries will be used. To facilitate data interpretation, this data should be collected using a standardized study protocol. In reality a 'one fits all' study protocol does not exist. Even though the general design can be standardized to a significant extent each country still has to plan and coordinate an HBM-study on its own (Joas et al., 2012; Becker et al., 2014; Casteleyn et al., 2015). These facts were the reason to develop the Phased Approach. The Phased Approach was based on the aforementioned experiences and established through a profound literature research, including other fields of surveys, e.g. clinical trials, complemented with information from project management. It compiles all necessary steps for study conduct and puts them into the chronological order.

For project management several commercially available project management tools exist but also the European Commission has developed an online available project management tool, called PM^2, available for free. It is based on standards and methodologies of globally accepted project management best practices and also on experiences from several European Commission projects (European Commission, 2018). As the idea of the Phased Approach was developed in the frame of the European HBM4EU-Project the PM^2 project management tool was selected to serve as a model for the Phased Approach.

In the field of project management, it is common to operate projects in several – often five or six - phases to facilitate a proper follow-up of the different tasks involved. They start with an initiation or project conception phase, followed by a definition/planning phase and moving on to the development/project launching and execution phase also called implementation/performance phase. Finally, there is the follow-up or project closing phase (Baars, 2006).

PM^2 includes 4 project phases: 1) Initiating Phase; 2) Planning Phase; 3) Executing Phase and 4) Closing Phase (European Commission, 2018: The PM^2 Methodology Guide v3.0). The activities of monitoring and controlling are part of each of the four phases. A description of the content of the five phases is shown in Table 1.

Besides the content of the single phases also their intertwining is of interest.

Fig. 1 demonstrates that in each phase one activity is predominant (e.g. in the Initiating Phase activities of initiating are predominant) but that these phase-related activities will also be executed in neighboring phases, i.e. there is an overlap of activities or some activities are continued in other phases, e.g. initiating activities are repeated in the Planning Phase. A project moves on to the next phase when the goals of the current phase have been reached (ideally, results are reported

Table 1
Descriptions of the project phases in the PM^2 project management tool.

Phase	Description of content
1. Initiating Phase	Define the desired outcomes. Create a Business Case. Define the project scope. Get the project off to a good start.
2. Planning Phase	Assign the Project Core Team (PCT). Elaborate the project scope. Plan the work.
3. Executing Phase	Coordinate the execution of project plans. Produce deliverables.
4. Closing Phase	Capture Lessons Learned and post-project recommendations. Close the project administratively.
5. Monitor & Control	Oversee all project work and management activities over the duration of the project: monitor project performance, measure progress, manage changes, address risks and issues, identify corrective actions etc.

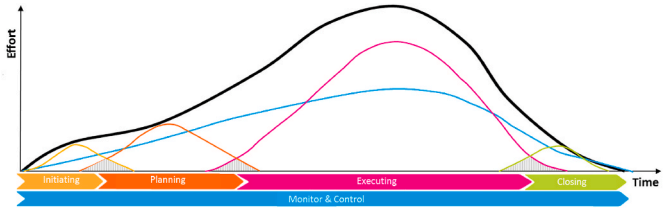

Fig. 1. The PM^2 project lifecycle: indicative phase overlapping and cumulative effort (source: The PM^2 Methodology Guide v3.0).

formally in a review). Although the Phased Approach intends to provide a step-by-step approach, an overlapping of some parts of a phase to the neighboring phases cannot completely be avoided and is partially necessary.

For the Phased Approach six phases have been developed. This was necessary to strengthen the step-by-step approach which is really helpful not to get lost in the manifold topics an HBM study comprises. As pointed out by the IEA (IEA, 2007) the cornerstone of epidemiological projects is the 'study protocol', an instrument widely used for epidemiological studies. It is a compilation and precise description of each issue necessary for the implementation, application, and evaluation of a study. Therefore, the Phased Approach is linked to the study protocol. Within this Phased Approach the key words of epidemiological studies (study design, selection of participants, recruitment, biological samples, fieldwork, questionnaires, analysis, interpretation and communication, and quality control) (Choi et al., 2014) are addressed as well.

3. Results

3.1. Overview of the Phased Approach

The Phased Approach breaks down the process of mapping a study into the 6 phases of (0) scoping and planning (1), preparation and testing, (2) initiation, (3) implementation, (4) conducting the fieldwork and starting with analysis and (5) reporting and evaluation procedures to close the project. This way, a step-by-step procedure becomes apparent and facilitates the development of an individualized study concept and the implementation of the study.

The numbering of the phases starts with "0" because there all general decisions necessary for the study conduct will be taken - this decision process is regularly not part of a study protocol where the Phased Approach is anchored.

Fig. 2 presents a rough overview of the 6 phases which are explained in more detail in the following text.

As an example, Fig. 3 provides an overview of a possible distribution of the workload (effort) for the six phases during a four-year period. In other studies, the duration of the phases will vary according to the survey design.

3.2. Phase 0 – Scoping and Planning

The Phase 0 sets the basis for all aspects of the study. Therefore, it is necessary to take the time for compiling all that is needed later on for the study and to prepare necessary decisions.

Decisions that have to be taken refer to three main questions:

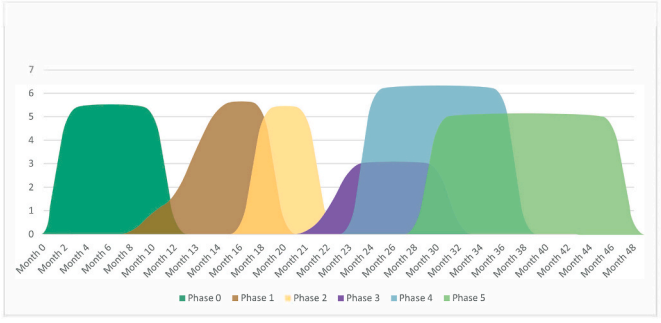

Fig. 3. Example of a possible distribution of the workload (effort) for the six phases during a four-year period.

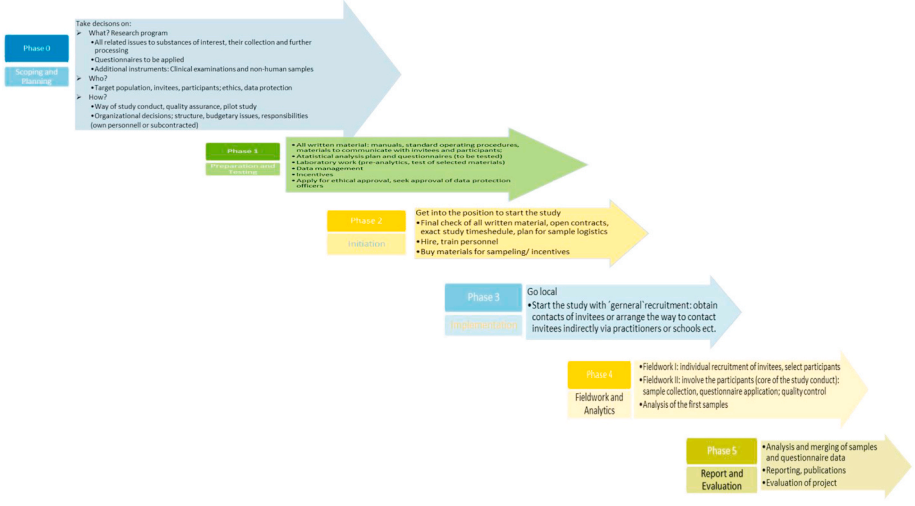

Fig. 2. Overview of the 6 phases of the Phased Approach.

a) **What?** Scope and hypothesis of the study and planned research program, including the substances to be analyzed, and instruments, i.e. human and additional environmental samples, clinical examination and questionnaires (Table 2)
b) **Who?** Target population and selected invitees (Table 3)
c) **How?** Organization and organizational structure of the study, including the distribution of responsibilities and resources (Table 5).

These questions need to be answered in detail, to disclose their interconnections, and to facilitate a proper study conduct.

This description of Phase 0 starts with a closer look first on the What? then on the Who? and finally on the How? questions. But the parts of the How? question dealing with responsibility and budget may be necessary to be decided in advance: who will take all these decisions, who will have to be included for taking specific decisions, which research program is possible with the available budget? All these decisions belong to Phase 0, but without knowing what exactly the study consists of budget is difficult to estimate, therefore, in this text the What? questions precede the How? questions.

Table 2
What? Things to consider and decide pertaining substances, questionnaires, and other additional instruments. Main question: Who?.

Substances of interest	Questionnaires (to elucidate exposure pathways and/or medical history)	Clinical examinations (e.g. lung function tests, weight and height measurements) and additional environmental samples of the homes of the participants (e.g. indoor or outdoor air samples, tap water, dust)
• Specified biomarkers (matrix/analyte): limits of quantification in the target population, time frame for sample collection • Analytical method: LOQ, certified reference material and standards, costs, etc. • Sample volume: for single analysis, repetitions and biobanking • Sample collection and storing material: material, volume, preservatives, control for background contamination, stability for biobanking (including labels), quality assurance aspects. • Processing of the samples during fieldwork (after receiving them from the participants) • Sample conservation and shipment • Sample reception and aliquoting process: number/volume of aliquots, labelling, criteria for acceptance/rejection of the samples • Qualified laboratories for the analyses (different labs may need different volumes)	• Content (e.g. living environment, diet/smoking behaviour, occupation, leisure time activities, health history, medication, socio-economic background; for substances with short half-lives questions that cover the last 24–72 h past urine collection) • Supporting questionnaires: recruitment questionnaire (meeting inclusion/exclusion (= eligibility) criteria, availability, history of contact); sampling questionnaires (i.e. period of sampling, recent exposure related to the target biomarker, etc.); interview guide (explaining the questions and possible answers for the interviewers or participants); non-responder questionnaire; satisfaction questionnaire. • Way of application (face-to-face interview, telephone interview, self-administered, paper and pencil, web based) (also view "How?")	• necessary research equipment (devices, sample collecting containers, communication material, personnel) • necessary validation procedures for new instruments (e.g. new questionnaires or devices) • to whom shall which instrument be applied (to all participants or subgroups?) • time needed for the run of these procedures during fieldwork

Table 3
Who? Target population.

Population aspects	Decisions related to involved population
Target population	general population, risk-exposure groups (occupational, hot-spot) children, adults, etc.
Definition of participants	Age, sex, number; eligibility criteria
Degree and direction of representativeness	National, Regional, local, and according to sex and socio-economic status; oversampling of a subgroup
Data to be collected (and stored?)	Organizational aspects of data management; data protection
Ethics committee for authorization	Requirements of the selected ethics committee, procedure, and duration of the decision procedures

3.2.1. *Main question: What?*

An HBM study is usually conducted either to obtain the distribution of certain substances of interest in the population or to estimate the exposure level of a specific target population. For both questions the substance(s) of interest is a starting point for all further decisions, as target substances have implications on the study design, the questionnaires, and the fieldwork. For example, the substance impacts the matrix of the biological sample to collect and the half-life of the target chemical in the selected matrix impacts the time of sample collection which again has consequences for the fieldwork (collection procedures differ for different matrices). Also, statistical power calculations used to detect the necessary number of participants for a representative sample are based on the selected substances. More detailed aspects connected to the substances of interest are shown in Table 2. Another What? - also shown in Table 2 - concerns the questionnaires that regularly accompany HBM samples, e.g. to elucidate the exposure pathways of the target substances. When additional instruments, e.g. clinical examinations, or environmental samples are included in the study, additional issues in the "What?"-category have to be thought of.

3.2.2. *Main question: Who?*

The decision on what to study is closely connected to the question on target population (whom). Some countries may start their decision cascade with the decision on the target population and continue with the decisions on the substances, both decisions are closely related.

Table 3 provides an overview of accompanying questions to the matter of the involved population.

To be able to apply the results of the study to the target population, not only the sample of invitees needs to be representative for the target population but also those who actually participate (the participants) have to represent the target population which can only be achieved if the sample was representative for the target population. Decisions pertaining the intended representativeness of the study have on the one hand a great influence on the way the fieldwork can be performed and on the other hand a high impact on data interpretation. Table 4 gives examples of how to obtain a representative sample in different population groups.

A good sampling method for selection of individuals if no population registry for a random sample is available or applicable is e.g. the stratified clustered multi-stage design. Via this design, geographical areas (stratification) are selected within a country. This can be applied if e.g. pregnant women shall be included and be approached when they arrive at the clinic before delivery. Within each of the geographical areas, primary sampling units (PSU), in this example the clinics (other examples: general practitioners, schools, work registries) are selected randomly, (or proportional to the number of individuals in these PSU). Furthermore, individuals are selected randomly within the PSU.

Once the target population is defined, in order to assess if an invitee can be included in the study as a participant or not, the definition of eligibility criteria is necessary. As this may have influence on the necessary efforts to obtain the desired number of participants, the decision on eligibility criteria is important at an early stage of planning of

Table 4
Methods for obtaining a representative sample in different population groups and their sampling frames.

Target population	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/ adolescents (separated by sex and/or age)	Population register (country, regional) Or stratified clustered multi-stage design	a) Obtain a random sample, keep track of non-responders and dropouts b) Extract from ongoing study
Vulnerable population (pregnant, newborns, seniors, etc.)	Patient files of clinics/ doctors/midwives	Obtain a random sample, keep track of non-responders and dropouts
Occupational population	Employment records, branch organizations, large cohorts	a) Prepare a list of eligible sampling units (workplaces) for random sample b) Extract from large database/cohort
Children/adolescents (different age groups)	Kindergartens/day care centers, or their groups Schools, vocational schools, or classes	Prepare a list of eligible sampling units (schools, day care centers) for random sample

Table 5
How? General decisions on way of study conduct, and on organizational structure, responsibilities, and budget.

Study conduct, general decisions	General decisions on organizational structure, personnel, and subcontracting
• Study design (cross-sectional, cohort, etc.)	• Organizational structure (Study Owner; Principal Investigator; Project Manager, managing team, etc.)
•Sampling frame for the participants (how shall participants be contacted?)	• Budgetary issues and allocation of financial, material, and human resources
• Timing and duration of the fieldwork of the study (season (how many seasons?)	• Personnel/responsibility for the preparation of all the written documents (like study protocol, Standard Operating Procedures (SOPs) for each instrument that is applied or developed, the data management and communication material for the participants, collaborating organizations and the general public
• Repeated (?) involvement of individual participants in the study	• Personnel/responsibility for organizational and pre-sampling procedures (e.g. mailing issues, preparation of sampling equipment/vessels)
• Manner to apply selected instruments (e.g. questionnaires); collection and drop-off of biological samples; additional physical measurements	• Personnel for execution of the fieldwork (nurses and/or professional interviewers), temporarily or permanent staff?
• Place of study conduct/participant involvement (participant homes; place of productive hours like schools, workplace, or the official head quarter for the study (examination center like in schools, clinics, town halls) or mobile centers	• Necessity for subcontracting (e.g. execution of fieldwork, laboratory work
• Incentives for participants (if decided to provide, what kind? reimbursement for travel costs and/or for spending time and samples): Information on individual and general study results; small gifts and certificates for participation	
• Quality assurance of the whole program and single steps (internal, external?)	
• Pilot Study – which instruments and processes shall be tested?	

the study. The eligibility criteria should consider general aspects of the study design, e.g. the age of the participants, and others that can affect the results such as illness, language difficulties, hot spot areas or working in specific enterprises.

A last but most important aspect pertaining the Who? is the compliance with ethical standards and data protection issues. The national and e.g. European regulations on ethical, legal and data protection issues have to be ascertained in an early state of the study planning to warrant proper compliance.

3.2.3. Main question: How?

Decisions on the How? already go deep into the details of a study. They involve the two aspects of 1) way of study conduct and general decisions necessary for this (based on the decision on the research program), and 2) organizational decisions (Table 5).

The type of **study** has big implications on each aspect of the study conduct but also on the scientific significance especially if elucidating causality is aimed at. Cross-sectional studies, for example, can answer policy questions related to the actual exposure levels of the target population but cannot be used to answer questions on causality (Kleinbaum et al., 1982). Decisions on the **sampling frame** detail how invitees can be contacted. The **timing** (seasonal aspects) and duration of the fieldwork have implications on the representativeness and on organizational aspects of the study. The target groups and their respective occupation have to be reflected (e.g. a study planned to recruit school children in schools should not start during holidays). Preferably, a study should cover all four seasons to avoid seasonal variation of the outcome measures. If this is not possible, potential biases have to be taken into account. Time needed for training activities of the field staff before and during the fieldwork has to be considered appropriately.

The decisions on the research program (What?) include decisions on the **instruments** to be applied, but it is also necessary to decide about the way **how** they shall be applied and how much time is needed, e.g. to answer the questionnaires. This duration has implications on the duration of the whole fieldwork. The more instruments shall be applied the more burden is put on the participants and this may also influence the participation rate (Mindell, 2015). Burden put on participants is an ethical aspect. Therefore, a balance between the necessities of the research program and the practical feasibilities of the study is necessary.

Decisions on the **place** of direct contact to the participants, private homes, or centralized examination rooms, also have implications on the organization of the fieldwork. It is advisable to offer alternative possibilities to comfort the participants, though it has to be checked if this is appropriate for the study instruments (home visits are necessary if e. g. indoor air or drinking water are to be collected by the field staff).

In order to obtain high participation rates, it is advisable to identify potential obstacles in the enrolment process early on and think about ways how these could be addressed. Progress of the recruitment should also be monitored throughout the fieldwork and adapted if necessary. If ethics committee allows, additional **incentives** can be offered such as financial and in-kind compensations. Incentives can be provided unconditional or conditional to participation. Type and format of incentives should be addressed in the first information for the participants (invitation).

Besides the quality control aspects pertaining the analytical and pre-analytical aspects of the samples and sample collection, **quality** control and quality assurance have to be applied for all instruments and the study as a whole. Internal quality control, e.g. for the fieldwork, can be performed by personnel of the unit of the institute or division not involved in the study. Additional external experts for quality control are especially advisable for larger research programs. Time for hiring and budget implications for these external experts have to be considered, too.

To warrant high quality results, it is advisable to conduct a **pilot study** to prove the interaction and functionality of the main instruments with a small group of participants. Conducting a pilot study will include

additional time and budget as all decision steps for the main study have to be repeated (in parallel) for the pilot study. But the pilot study provides information on the feasibility of the actions and acceptability of measurements by participants and thus has implications to the costs and the quality of the results of the main study to a considerable extent (Becker et al., 2014; Biemer and Lyberg 2003).

Additionally, and finally, decisions are also necessary on **organizational issues**, pertaining the structure and the personnel responsible for the main parts of the study (Table 5).

To have a clear **structure** and a clarification of the sharing of **responsibility** is extremely important for the success of a complex study (Tolonen, 2016). According to project management, the establishment of a project team is a necessary activity to effectively plan and execute a project (Weber and Cobaugh, 2008). This supports the inclusion of different perspectives while setting up the research plan and planning the study. It plays an important role in ensuring the successful conduct of the project and for the concrete tasks, e.g. the preparation of all necessary (written) material, but also for decisions in case of unforeseen events. Allocation of human resources is, like material and financial **resources,** included in budgetary decisions. Mostly the **budget** has a steering (often limiting) function on the structure, the number of participants involved, the instruments applied, the duration and organization of the fieldwork and the **subcontracts** or additional permanent or temporary **staff** required.

The How? Questions also tackles the question on **responsible personnel** for developing the written material. Indispensable for the quality of an epidemiological study is the proper elaboration of written instructions, summarized in the **study protocol** and detailed in the Standard Operating Procedures (**SOPs)** and **questionnaires**.

It will be necessary to develop diverse **communication** material, as communication is key to ensure a successful contact to the participants and to reach acceptable participation rates (Exley et al., 2015; Tolonen, 2015). These might not only be written material but can also take the shape of information meetings for potential participants, informational videos, social media presence or websites. For this or, e.g. for a potential new corporate design for the study (a logo), subcontracts/tender procedures may have to be set up.

Project management guidelines recommend preparing a timeline for the whole project.

This could also be part of the Phase 0 or a first action of Phase 1.

After these final decisions have been taken, Phase 0, the Scoping/Planning Phase, ends. All theoretical considerations are now done. At this point the next phase starts with the elaboration of more details.

3.3. Phase 1: Preparation and Testing

The main focus of Phase 1 is on arranging those instruments and materials that need preparation and/or testing before they can be used for the study. If not already done in Phase 0, a first task of Phase 1 is the fixing of a **timeline** for the project. Also, it has to be safeguarded that the progress of each task is trackable (with indicators, milestones) to be able to steer the process.

The first emphasis should then be put on the **written materials** because much of this is needed for the **approval of the study by an ethics committee** and the acceptance of the data protection officer. Both have to be approached in this phase and their approval carefully reviewed as it is a prerequisite for each study. Additionally, translations into different languages might be necessary which will also take some time.

The preparation of a **Fieldwork Manual**, a collection of all written materials that are necessary for the fieldwork should start.

The development of **questionnaires** is in itself a complex and time-consuming endeavor. Therefore, it is helpful to rely on already used and tested or validated questionnaires or questions whenever possible. A **statistical analysis plan** can help to streamline the questions to the research plan. Each question needs a justification or rationale for being asked and this background information should be put together in an **Interviewer Manual** if the questions are administered by interview. Otherwise this background information can be used for the elaboration of the information material for the participants (FAQs). Before questions or questionnaires can be applied to participants it is necessary to test them with at least 15 volunteers (Perneger recommends 30 (Pernegger, 2015)) not only for the validation of the questions, but also to get an impression on the time needed for answering. This participant burden is of interest for ethic committees. If questionnaires are administered by computer assistance (CAPI/CATI/CASI/CAWI), respective codebooks for the programming of the questionnaires for computer programs have to be developed.

Another part of the **communication material** that should be prepared in this phase are all other information materials about the study itself (information leaflet, flyer etc.) and instructions for study participant, e.g. handling and storage of the samples the participants have to take themselves, such as the first morning urine samples.

First ideas for the communication of the study to the target population should also be developed in this phase.

Suitable **communication** is key when aiming at ensuring a successful contact to the participants and to reach acceptable participation rates. Therefore, already at this planning stage implications of the communication aspects are important to reflect (Exley et al., 2015; Fiddicke et al., 2015).

Besides these written materials, **other preparatory work** should be started in this phase as shown in Table 6.

3.4. Phase 2: Initiating

Phase 2 comprises the concretization of the work ahead. All what is needed to be able to start with the fieldwork has to be turned into practice, initiated, e.g. material has to be bought or laboratories contracted, and final decisions regarding fieldwork, laboratory work and data management have to be made and respective measures taken. At this point, all prerequisites for the study, like ethics authorization and data protection issues are already solved.

Table 7 provides a detailed overview of the tasks of Phase 2.

The **Fieldwork Manual** (and other written material) has to be checked for necessary updates (e.g. printing errors etc., but attention not to get into conflict with the already received ethical authorization) so it can be used for the **training** of the field staff. Training workshops provide an overview on the study itself, its background, the background of

Table 6
Preparatory work to be completed in Phase 1. After all this preparatory work is finalized, or at least well on track, the next, more detailed work can start in the Phase 2.

Data management and incentives	Laboratory work
• Develop a data management plan • Creating a database for the contact details and the recruitment procedure • Creating a separate database for the questionnaire data and analytical results •If non-monetary incentives are planned their design should be prepared • For monetary incentives, a reception sheet should be prepared	• According to QA/QC-criteria qualified laboratories for the selected biomarkers have to be contacted or a tender process be prepared. • Test the planned collection materials on their usability, e.g. tubes and vessels are free of contaminants, labels are suited for the sampling and storing conditions (temperature, humidity, etc.) • Prepare a sample reception protocol to be filled in by involved laboratories, necessary to control the integrity of the packaging and the conditions of the sample tubes and vessels (respect the General Data Protection Regulation) • **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.

Table 7
Overview of the tasks of Phase 2.

Remaining issues to get into the position to start the study
• Updates of the Fieldwork Manual with all SOPs, communication material and questionnaires.
• Engage qualified interviewers/fieldwork staff.
•Organize and perform the training of the interviewers/fieldwork staff.
• Decision on exact starting date and duration of the fieldwork, provide a route plan for the visit of included cities (sampling or study locations).
• Organize/purchase the incentives which have been selected for the participants (books, bags, etc. with study logo) and a reception sheet for monetary incentives.
•Purchase 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 sampling (clean with acid solution, label it, etc.). Also, material for sample transport to the laboratory or biobank have to be considered.
• Fix relation to targeted laboratories, sign contracts. Define the date and delivery format for the analytical results: type of file, units, report about the internal quality controls applied, etc.
• Provide packing lists and prepared material for the field staff.

the questions and specific topics and explain the details of the workflow (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.) The training should also provide hands on training, e.g. pertaining the samples and sampling and conducting interviews.

Phase 2 also includes the creation of a detailed **fieldwork schedule** for the field staff with start date, end date and route plans concerning the involved study locations (towns, cities, or regions where the fieldwork will take place).

The decisions pertaining the **incentives or compensation,** be it monetary or non-monetary, will need concretization in terms of buying (e.g. small gifts) or designing (certificate).

The fieldwork logistics have to be planned and prepared including obtaining required devices and materials, their temporal storage, and transport to and from the fieldwork location.

Laboratory equipment plays an important part in this phase. If the collected samples shall be (partly) processed directly in the field, it is necessary to ensure that minimum laboratory equipment will be available, e.g. refrigerator, centrifuge to warrant optimal conservation, and appropriate facilities to avoid the contamination of the samples.

If transport of samples is foreseen, the packaging must fulfil the regulations (local and general) concerning the shipping of biological material. If the transport will be done by couriers, the details what exact their service covers needs to be checked in advance to prevent loss of samples.

If external laboratories are involved (selected in Phase 1), contracts need to be negotiated, set up and signed. These contracts should also include the date of finalizing the analyses and the date and format for reporting the results.

To further support the field staff or interviewers, a checklist with all materials and devices for a study visit can be compiled.

All databases necessary and a data management plan have already been developed in Phase 1. Final test runs for these plans and databases can still be done in this Initiation Phase.

3.5. Phase 3: Implementation

Phase 3 deals with the 'general' recruitment. It pertains all that is needed to reach the target group that shall be involved in the planned study. It only begins some two-to-three weeks before the start of the fieldwork, which is defined as the direct involvement of the participants. What exactly is necessary in this phase varies according to the way volunteers will be included in the study.

In general, for population based representative studies, an invitation to all persons of the selected sample of the sampling frame fitting to the target population is necessary. Often contact details are obtained from sampling frames, like population registries of selected towns or lists of pupils of selected schools. Another way is to contact selected schools to prepare teachers to be the promotor of the study in selected classes or to inform the parents via the school internet or special events that their children will be invited. Physicians, midwives, or selected maternities are sometimes approached to reach special groups of probable participants. The professionals need to agree and be prepared to forward invitations to the persons that fit to the target group. Finally, as a result of this 'general' recruitment, one of the two options has to be accomplished either a list of potential participants to whom invitations can be sent shall be available or counterparts for direct participant contact are established – so the sample of the invitees is prepared.

Timing of this 'general' recruitment is a sensible issue. It should not be done too long in advance before the fieldwork shall start because invitees might change addresses or approached counterparts are no longer available. This risk increases with the timely distance between searching for addresses and sending individual invitations.

If addresses of individuals have been collected, they then can be transferred to the databases set up in Phase 2. Additionally, each individual is assigned a study-specific ID number which serves for pseudonymization of results. During this process and from here on out, data protection always has to be ensured.

During this Implementation Phase also the visit at the first study location (i.e. the region or city where the study will take place) is prepared. For example, the place or rooms that serve as examination centers have to be rented as well as rooms for field staff. Examination centers serve the needs for the study, i.e. consist of separate rooms (as waiting room or reception, room for interviews, room for exercises, sanitary facilities, etc.) and can be in schools, town halls, or clinics etc. They should be easily accessible and are necessary in each study location. If overnight stays of the fieldwork staff are necessary, this has also to be arranged.

This is also a good period of time to raise awareness for the study and start communication with the target or additionally the general public about the study at the sampling location with the aim to increase the participation rate.

Finally, the laboratories that will analyze the biological samples have to be informed about the upcoming start of the fieldwork so that they are ready to start with the first analysis.

3.6. Phase 4: Fieldwork and Analysis

Fieldwork starts with the direct contact to the individual participants. The first part of fieldwork (Fieldwork I) comprises the individual recruitment and starts directly after the general recruitment has provided the contact details of those who shall be invited or has informed about the way how to approach them.

Invitations can now be sent, or direct contact be established. Invitees shall be provided different ways to articulate their acceptance or rejection of the invitation (e.g. personally, via phone, a reply card, email, or online tool). For organizational issues and to have the ability to calculate response rates it is necessary to keep track on the answers. Volunteers need to be contacted and checked for eligibility criteria. Those who will finally be included in the study, the participants, will be informed on their participation and probably sent detailed information or additional materials necessary for the study. Appointments for personal interviews or clinical examinations will be fixed.

Individual recruitment can be very time consuming, as it is necessary to grant several days for response and provide several reminders – how many should be detailed in the Fieldwork Manual.

In those cases where invitations have been sent but invitees did not react the field staff can still try to recruit them personally. For statistical reasons (representativeness) it is important to try very hard to reach each randomly selected participant (see Fieldwork II below).

In case a potential participant refuses to participate, a non-responder

questionnaire should be administered to be able to compare non-participants with participants to check for potential response bias.

During the whole fieldwork procedure – until the participants have received their individual results - a phone number and an email address of the general study office as contact address has to be provided.

The second part of fieldwork (**Fieldwork II**) is the core element of the study. Here the participants are directly involved in the study: samples collected, questionnaires are applied, clinical examinations are carried out and afterwards incentives and results provided - all depending on the instruments decided upon in Phase 0 and precisely laid down in the Fieldwork Manual.

An example for a schedule for the fieldwork procedures at study locations could be: Upon arrival at the study location the examination center is furnished with study equipment and devices. Before the visit of every single participant, the material (such as interviewer identity card, papers, laptop, additional sampling vessels, incentives etc.) is checked, prepared, and stocked up. On arrival of a single participant, the field staff checks and accepts the declaration of informed consent from the participant. Only then the other instruments of the study are applied, e. g. the questionnaire can be filled out, measurements and samples taken. In case not all parts of the fieldwork could be completed at once, an additional visit in the next few days should be offered to the participant.

If the participant involvement takes place in the participants' homes special care has to be taken. Respect for the residents and close observation of household etiquette is strongly recommended to avoid negative effects on participation rates.

Each visit needs to be well documented with details concerning duration, completion, handovers and consent, and all procedures accompanied by quality control measures to warrant high quality of the received results.

Procedures for **handling of the samples** collected from the participants have been laid down in the Standard Operation Procedures (Phase 1 and 2). Now, in this phase those SOPs have to be followed closely, e.g. aliquoting of the matrices, preparing for shipment or storage.

If the study includes more than one study location all procedures will have to be repeated.

In parallel, the laboratories can **start analyzing samples** to be prepared to report the results back to the participants (as laid down in the ethics documents).

The managing site of the study (Principal Investigator, Survey Office) has to supervise the work of the field staff and to provide help and advice if necessary. Furthermore, internal quality control for fieldwork has to be established 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 to maintain the quality of the fieldwork.

Another important issue pertains the safeguarding of data protection. E. G. in Europe, the GDPR sets strict rules on the handling of sensitive personal data. Safeguarding compliance with the GDPR is a prerequisite for every study to be conducted in Europe.

3.7. Phase 5: Reporting and Evaluation – Leading to Closure

After the fieldwork is completed in one study location and the results of the sample analyses have been checked, the participants have a right (e.g. based on GDPR) to have their individual results reported back to them, preferably accompanied by some explanation if the values are prone to raise concern. After the fieldwork and the sample analyses are completed in all study locations results of the different instruments have to be merged and checked, participants who can count as a case have to be defined, i.e. who provided the information defined as indispensable (e.g. on smoking, alcohol/drugs use, diet, number of years living in the sampling location etc.). In the following, the cases are statistically analyzed according to the research questions. Only then advice for the (general) public and policies can be provided.

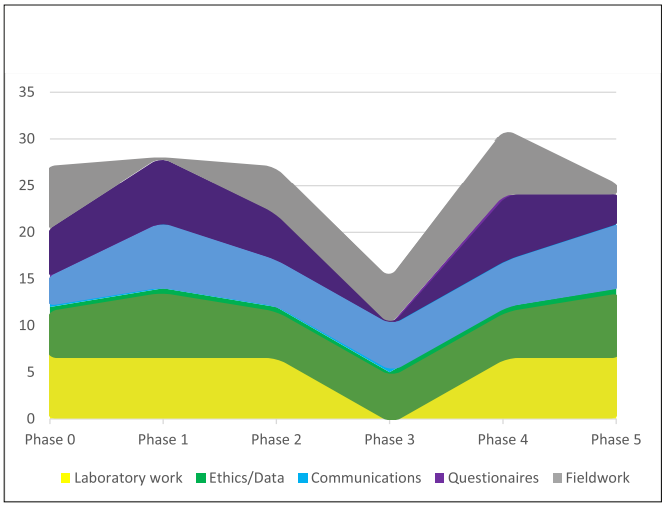

Fig. 4. Example for a schematic overview on the distribution of efforts of the different parts involved in study conduct.

Each part of the study should finally be evaluated – to support the conduct of following studies.

This phase is to close the project – all remaining activities, like publishing results, reporting back to funding organizations and finalizing contractual obligations are part of this last phase.

The workload of the different parts involved in a study, like laboratory work, ethics and data management activities, preparation and use of communication materials, questionnaire development and application and fieldwork preparation and conduct are unequally distributed across the different phases. Fig. 4 provides an example for a schematic overview on the distribution of efforts of the different parts.

4. Discussion

Epidemiological studies consist of many elements and have high budgetary implications. These rise even more if it concerns a human biomonitoring study which includes not only the interview of volunteers but also biospecimen to be taken and analyzed. Given the wide range of biomarkers, biological matrices, analytical methods and influencing factors, the study design is a critical aspect in the efficient use of HBM in risk assessment (Choi et al., 2014). The planning of such a study should therefore be comprehensive and include all aspects such as research subjects, materials to be included, target population, selection of participants, communication with all interested groups (stakeholders), biological analyses, data management, scientific publications, policy advice and first of all ethical and legal considerations. It is possible to find scientific publications on all of these single aspects and there are some guidelines available for good epidemiological practice. Also, several countries that run regular HBM programs have informed about their national strategy on human biomonitoring Belgium (Reynders et al., 2017; Schoeters et al., 2012), Canada (Haines et al., 2017), Czech Republic (Cerna et al., 2007, 2012), Denmark (Thomsen et al., 2008), France (Fréry et al., 2012), Germany (Kolossa-Gehring et al., 2012; Schulz et al., 2007). But none of these publications provide details on the complex procedure of planning a study or inform about an advisable

order for the planning of all the involved aspects.

The Clinical Trials Transformation Initiative (CTTI, 2015) has developed quality-by-design principles for clinical trials to remove errors with meaningful impact on the credibility of the results. They aim at promoting critical thinking about trial design to prospectively build quality into the scientific and operational design of clinical trials rather than relying on retrospective scientific reviews (Meeker-O'Connell et al., 2016). These principles also include the study protocol design which contributes to high quality results if it is designed appropriately.

A good example for the planning of studies is available for the European Health Examination Survey (EHES). The EHES Manual (Tolonen, 2016) provides guidelines for the implementation of standardized national health examination surveys (HES) in European countries but can also be a reliable source for studies in other fields. EHES proposes a circular planning procedure, consisting of 6 parts: (1) defining the scope of the study; (2) planning and preparation; (3) pre-testing and piloting; (4) final survey design, planning and preparing; (5) fieldwork and data collection; and (6) data file construction, analysis and reporting. Quality assurance aspects link these individual parts. After all is done, the planning for the next study can start in the same order. Tolonen also recommends links to project management tools (Tolonen, 2016).

A similar attempt has been undertaken by Statistics Canada 'Survey Methods and Practices' providing insights into survey practices (Statistics Canada 2003 and 2010). Like the EHES Manual (Tolonen, 2016) and the publication by Becker et al. (2014), all provide valuable information on alternative approaches for epidemiological studies, providing background information for an information-based decision making on nearly all aspects of study conduct.

Further in-depth information on study-design is available, e.g. in Blair and Czaja 2014 and Flower 2014 (Blair and Czaja, 2014; Flower, 2014). Both books elaborate on general and specific issues on survey design for research and provide a comprehensive overview of the sources of error and the range of methodological issues in survey data collection. The US National Research Council (National Research Council, 2006) describes in detail considerations in the design of biomonitoring studies and provides with this highly valuable information on several aspects of biomonitoring studies which could help the decision-making processes.

Conducting a study involves many activities and several of them have to be started in parallel. None of the above-mentioned publications promote a structured concept or process for the planning of a study. To avoid not considering important aspects up front - and sometimes it might be too late to change things during the run of a study - the idea to develop a stringent concept for the planning of epidemiological/HBM studies arose and was turned into reality with the Phased Approach.

As stated above, HBM studies need experts from different fields, i.e. multi- or interdisciplinary teams will work together. This in itself may pose some problems to the success of the project. To overcome such problems, Tobi and Kampen developed a Methodology for Interdisciplinary Research (MIR) framework (Tobi and Kampen, 2018) based on a process approach which puts the common goal of the researchers at the center of the project thus creating different phases of the process: first the research team discusses about the different parts of the design of their study and only then the study is executed. During the first discussion of the conceptual design of the study the 'why' (research objective) and 'what' (research question) of the research is decided. Then, the team discusses the technical design of the study ('how': study design; instrument selection or design; sampling plan; analysis plan). The execution of the work (including fieldwork) only starts after decisions of the complete research design have been taken (Tobi and Kampen, 2018). This concept is closely related to the handbook of project management from Baars (2006), the definition phase is also addressed as "What?" and the Design phase with "How?". The MIR framework and the Phased Approach have the technical part – answering the question of "How?" in common, it deals mainly with fieldwork. Whereas the "What?" describes the research question (MIR framework) and the research program (Phased Approach), respectively. This discrepancy can be explained with the fact that the Phased Approach does not include an extra phase for elucidating the research question as it was developed for studies conducted in the frame of HMB4EU where the research question is to a great extent already decided upon on the level of the HBM4EU project. MIR framework and Phased Approach do have in common that first decisions have to be taken (Phase 0) and only afterwards the execution of the study is prepared and started. The Phased Approach was originally developed for (preferably population representative) HBM studies conducted in the frame of the European Joint Program HBM4EU though it can be adapted for other epidemiological studies. Conducting studies in the frame of HBM4EU has the consequence that the scope of and the research question for the intended study has to be within the scope of HBM4EU, i.e. is restricted to certain substances and age groups. Additionally, the time frame for the study is set. In consequence the project conception phase, defining the scope and developing the research questions is no single phase in the Phased Approach but is included in the scoping/planning phase (Phase 0). This can be adapted if the Phased Approach is used in other contexts.

5. Conclusion

Complex (HBM) studies need considerable financial, material, and human resources. This obliges those responsible for the planning of a study to search for methods that support the ideal allocation of the available resources. A study can be dealt with like a project and therefore tools of project management can be applied. Project management, e.g. PM^2 of the European Commission, separates the work within the project into several phases, like initiating, planning, executing, and closing phase which serves a structured procedure and a suitable allocation of resources. Several years of experiences in planning different HBM studies lead to the introduction of project management tools into study design. This is done with the aim to support new researchers in the field of HBM studies in conceptualizing resource efficient studies. Resources in terms of personnel and applied instruments can best be made use of if the concept of a study is thoroughly thought of. Therefore, the proposed Phased Approach lists all aspects which may occur in the later stages of a study already in the first phase as decision points. Only after all decisions are taken, the concrete work for the planned study shall start in a step-by-step approach. Following the Phased Approach can lead to a well-planned study resulting in highly valuable quality assured results with optimized allocation of resources.

Declaration of competing interest

Declarations of interest: none.

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