PROTOCOL FOR SURVEY STUDY

"A CROSS-NATIONAL SURVEY ON THE IMPLEMENTATION AND MAINTENANCE OF THE ATC/DDD CLASSIFICATION SYSTEM"

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Abbreviations

ATC: Anatomical Therapeutic Chemical

DDD: Defined Daily Dose

DPP: DDD Per Package

EMA: European Medicine Agency

EuroDURG: European Drug Utilization Research Group

FDA: Food and Drug Administration

ISPE: International Society for Pharmacoepidemiology

NDC: National Drug Code

WHO: World Health Organization

Executive Summary

This protocol describes the design, implementation, and analysis of a cross-national survey aimed at collecting information from nation-level experts on how and if the ATC/DDD Classification System is actually implemented with respect to WHO recommendations. In particular, the survey will collect nation-specific information on the actual methodology and governance for the creation and maintenance of a reference national registry in which the dictionary of medicinal product packages is linked to the ATC/DDD index and corresponding DPP, as well as on how such a registry is made available to users.

The survey will be administered to both a convenience sample of nation-level experts identified within the ISPE and EuroDURG community and also to a sample of experts identified through snowballing. The targeted nation-specific experts will be both scientists who use the ATC/DDD Classification System for pharmacoepidemiology/drug utilization research and any other professional figure who might be involved in the governance and/or the applied methodology for its implementation and maintenance (e.g. regulators, administrative and ICT personnel, terminologists, scientists involved in drug statistics procedures).

The analysis of the collected data will provide a picture of the actual status of the implementation of the ATC/DDD Classification System around the globe. Moreover, it will allow for the identification of good practices and possible sources of misalignment across countries in terms of implementation and maintenance of the ATC/DDD standard, also documenting existing differences in the transparency and reproducibility of such processes.

The result obtained will be used to provide recommendations useful both for countries that have the ATC/DDD Classification System already in place and for those that intend to implement it, with the final aim of fostering reproducibility, comparability, and transparency of pharmacoepidemiology and drug utilization studies that make use of the ATC/DDD Classification System.

1. INTRODUCTION AND STUDY AIM

Since 1996, the Anatomical Therapeutic Classification(ATC)/Defined Daily Dose (DDD) methodology has been adopted and proposed by the World Health Organization (WHO) for global use as a standard tool for monitoring the utilization of medicines(1). The ATC classification system allows classifying active substances according to the organ or system on which they act and according to their therapeutic, pharmacologic and chemical properties. The ATC classification is based on a hierarchy with five different levels of granularity, where the 5th level identifies the chemical substance(2). The DDD is associated with 5th level ATC codes and is relevant to different routes of administration. It is defined as "the assumed average maintenance dose per day for a drug used for its main indication in adults"(3). The measure provides a standardized way to describe an amount of a specific substance regardless of formulation, strength or package size. The DDD ought not to be interpreted as equipotency between substances without a separate situation-specific validation.

Both the ATC codes and DDDs are assigned by the WHO Collaborating Centre based in Oslo, Norway, which also releases updates of the ATC/DDD index annually. However, the assignment of DDD is not exhaustive: for instance, for 5-level ATC codes concerning dermatological drugs, sera, contrast media, vaccines, and drugs with significant interindividual dosing variability (like many antineoplastics), there is no assignment. For some, (e.g. combination products containing hypertensive, antiglaucoma preparations) the WHO collaborating Centre issues recommendations for national experts to assign the corresponding DDD(4), although this requires manual input which thus might be prone to errors.

By linking the fifth level ATC code and corresponding DDD to the relevant medicinal product package, the 'number' of DDDs per package (DPP) can be also calculated and used for drug utilization research and monitoring. DPP is also a commonly used measure of the number of days of supply (sometimes DDD per unit of presentation might be used instead). In fact, DPP is often used for calculating the duration of episodes of treatment and assess exposure in pharmacoepidemiology studies as well as adherence and persistence in drug utilization research(5,6). Beyond ATC and DDD, the calculation of DPPs requires the application of formulas based on the medicinal product characteristics (e.g. route of administration, pharmaceutical form, number of units presentation, concentration)(4), which are not necessarily stored in a standardized manner in all countries, thus hampering reproducibility and comparability. However, advances were recently made in the implementation of ISO/CEN standards for the global identification of medicinal products, that were achieved by joint action of the European Medicine Agency (EMA), Food and Drugs Administration (FDA) and WHO Uppsala Monitoring Center for Pharmacovigilance and the EU Horizon 20/20 Action Program UNICOM(7). This provides an opportunity to facilitate international comparisons and validation of national implementation of the ATC/DDD index.

The task of establishing a register linking a national medicinal product dictionary to the most updated release of the ATC/DDD index and correctly calculating the number of DPP, is

recommended to be executed at a national level(4) in order to avoid misalignment within the same country. This becomes concrete by establishing a national medicinal product dictionary that links each unique medicinal product package identifier to the corresponding ATC/DDD/DPP, preferably publicly accessible and verifiable by national and international scientists(8). Transparency of the methodology for creating and updating this reference resource is fundamental for its reproducibility and validation(9). It should be open to international scrutiny by the scientific community and hence would require each country to make the updated file link publicly available. In fact, divergent ATC/DDD versions, divergent assignment of DDDs for combination products, and the use of unofficial or national DDDs have been already documented as methodological issues for the collection of comparable data on drug use across countries(10–13).

Lack of consistency in the implementation and maintenance of the ATC/DDD Classification System can hamper reproducibility of studies that make use this methodology for either the generation of drug utilization statistics or for creating study variables (e.g. exposure, adherence, and persistence to treatments, outcome or confounding variables).

The aim of the present research is to collect nation-level information on the actual methodology and governance in place for the implementation and maintenance of medicinal product dictionaries linked to ATC/DDD/DPP, and on the availability of such registries in the public domain.

This initiative meets the ISPE strategic goal of building expertise by developing resources that support researchers in pharmacoepidemiology worldwide, and is endorsed by the European Drug Utilisation Research Group (EuroDURG)(14) and the Drug Utilization / Health Services Research Special Interest Group of the International Society of Pharmacoepidemiology (ISPE DUR SIG)(15), which will both actively contribute to the project.

The present survey-based study is part of the project “Exposure to Medications Measured using the ATC/DDD Classification System (EMMA)”, a spontaneous initiative of international researchers that aims to improve the reproducibility, transparency and reporting and of drug utilization and pharmacoepidemiology studies that make use of the ATC/DDD classification system.

No funding was received for the execution of this study.

2. METHODS

2.1 STUDY DESIGN

A cross-national, survey-based study will be performed to collect nation-level information on the implementation and maintenance of the ATC/DDD Classification System from nation-level experts (16,17).

The survey will be created and administered on-line using the RedCap software (18,19). The

survey instrument will be adaptable to different types of respondents (i.e. “researcher/user” and “regulator/technician”, see also section 2.2) and national contexts (i.e. countries with/without a national dictionary of Medicinal products and/or with/without ATC/DDD Classification System already linked to the latter). The survey will be structured to allow answers to trigger additional branches containing field-specific questions (for example, questions related to the methodology for the assignment of ATC codes and/or DDDs that are not officially defined by the WHO). The primary language of the questionnaire will be English. The questionnaire will be also translated into Spanish and French. Translation in other languages will be considered whenever explicitly required. Back-translation will be performed to ensure accuracy of translation.

Subsequently, the survey will be piloted through administration to a sample of study members and other selected external recipients representing at least one country already known to have already implemented the ATC/DDD Classification System at national level and one country that did not, respectively. For both countries selected for the pilot phase, at least one response per role among “researcher/user” and “regulator/technician” should be obtained. This process aims to test methods to increase survey response and identify practical errors (for example, incorrect implementation of the functionalities of the chosen survey tools, broken hyperlinks, error in the text of the automatic messages).

2.2 Study Population and sampling frame

The study population will be represented by nation-specific experts of the ATC/DDD Classification System.

Such experts will be identified among both scientist who use the ATC/DDD Classification System for pharmacoepidemiology/drug utilization research and other figures who might be involved in the governance of its implementation and maintenance (for example regulators, administrative and ICT personnel, terminologists, scientists involved in drug statistics procedures).

An opportunity sample with additional snowballing will be identified (20). Therefore, the sampling frame of the survey will correspond to a list of nation-specific experts a priori identified within the list of members of the ISPE and EuroDURG communities and an additional list of additional contacts identified through snowballing. In particular, connections of members of the ISPE and EuroDURG communities will be leveraged to identify additional contact of nation-specific experts of the ATC/DDD Classification System also for countries that are not represented in the above-mentioned communities. Moreover, additional contacts of nation-specific experts will be possibly identified among those suggested by recipients of the survey invitation letter (see Appendix 1). In fact, recipients of the survey invitation letter will be requested to suggest additional contacts of nation-specific experts to which the study investigators will also administer the survey whenever deemed

useful for the purposes of the study.

2.3 Sampling Method

Since we expect that some geographic areas and roles will be more represented in the sample frame (for example, researchers), we will use respondents' role, defined as "researcher" and "regulator/technician", and country of origin to create a stratified sample frame.

A list of email addresses of survey recipients will be organized according to role, i.e. "researcher/user" and "regulator/technician", and country. Therefore, in order to maximize coverage and, at the same time, increase efficiency and avoid an overload of administrative burden, a target number of a minimum of 2 and a maximum of 5 recipients per role and country will be considered.

Collecting information from respondents with different roles for the same country will allow triangulation (questioning persons with different perspectives) to determine the true situation in a country. Multiple conflicting answers to the same questionnaire item will be considered as evidence of lack of a clear reference source of information in the country. Indeed, respondents will be recontacted whenever deemed necessary to ensure validity of answers (e.g. exclude misunderstandings).

Our aim is to obtain a sample of survey respondents that covers as many countries as possible around the globe. Ideally, we aimed at collecting information from at least 1 recipient per role and country from at least 2 countries per continent.

Notably, the aim of the sampling method is not the selection of a representative sample of an underlying population, rather it is interviewing different stakeholders about a single truth, to be elucidated by comparing and contrasting the different perspectives of that truth.

The survey will be conducted online, in English, using the RedCap software(19), and in compliance with the GDPR. The questionnaire will be also translated into Spanish and French. Translation in other languages will be considered whenever deemed necessary. Back-translation will be performed to ensure accuracy of translation.

Sample members will be informed of our intention to invite them to participate via email prior to data collection(21). The email will include an explanation of the initiative and its purposes, as well as information on how the participant was selected. Instructions on how to opt out will also be provided. Participants who decide to opt in will be allowed to access the survey or receive a reminder a few days later.

The distribution of the survey and data collection period is expected to last for about 4 months, from June to the end of September 2024. The survey recipient sample will be

reached out with pre-notifications sent out. Non-responders will be followed up with a maximum of 4 reminders, one per week. All persons contacted will be allowed to opt out and be removed from the mailing list at any time.

Increasing response

The survey will be designed following recommendations for increasing response rate (21), such as reducing survey length and complexity of the answers, increasing specificity/complexity of questions only if suitable to previous answers (e.g. an additional branch containing a field-specific question will be triggered depending on the answer to the previous question), reducing requests for personal or sensitive information, translating both the invitation email and the survey also in Spanish and French.

In particular, we expect that the selection of a sample of recipients who are really knowledgeable about the processes of interest will substantially increase response rate. Therefore, considering the target sample of survey recipients (i.e. users or contributors of the ATC/DDD standard), the nature of the survey content itself is expected to incentivise response.

Endorsement of the EuroDURG and ISPE DUR SIG will add legitimacy to our request for information.

Contact details will be also provided to allow respondents asking study investigators any additional questions, clarification, or concerns with respect to the survey.

2.4 Inclusion/Exclusion Criteria

Respondents will be requested to answer at least one of the required items (see section 2.5)) of the questionnaire to be included in the study.

Responses to the survey submitted after the end of the survey collection period (to be defined) will be excluded.

2.5 Survey Design, content, structure and analysis

The survey design will be inspired by the “Guidelines for ATC classification and DDD assignment” (4) and the “Recommendations for national registers of medicinal products with validated ATC codes and DDD values” from the EURO-MED-STAT project (8).

The survey will have the following structure (see also Table 1 below):

1) Introduction to the project: information given in the initial invitation email will be provided again at the start of the survey through a brief overview of the survey purpose.

2) Questionnaire-based collection of information organized in 5 sections corresponding to the following 4 main topics:

1. Respondent information

2. Availability of, and accessibility to, a national medicinal product dictionary linked to ATC/DDD Classification System

3. Governance for the implementation and maintenance of the Medicinal Product Dictionary linked to the ATC/DDD Classification System

4. Methodological details for the implementation and maintenance of the Medicinal Product Dictionary linked to the ATC/DDD Classification System

Within each topic of the questionnaire, however, the actual items that will be included in the final version of the questionnaire will be possibly updated/modified/changed according to the input from researchers contributing to the development phase and then refined according to feedback collected from the pilot phase. Survey items will require mainly closed-ended responses. Open ended answers will be allowed for additional clarification or for providing documents/references. The questionnaire structure and items are available in the Appendix, section 6.1.

Information provided in free text will be analyzed and summarized manually by researchers participating in the execution of the survey.

The survey will be designed to ensure that it will take no more than 15-20 minutes to complete. This will be also tested during the pilot phase.

Information collected will be used to describe the actual governance and methodology of the implementation and maintenance of the ATC/DDD Classification System across countries, identify possible sources of misalignment and provide recommendations for best practice.

Table 1. Rationale and items for Survey Topic Areas

Topic/section	Description	Rationale	Items (allowed answer)
1)Respondent Information	Country Role[1]	These variables will be used to collect country specific information and make distinction on the role[1] of the respondent with respect to the ATC/DDD Classification System. It might also be used to branch respondents through the survey where certain questions are/are not pertinent, for example, role-specific.	1.1)What is the country for which you can provide information that is relevant to the objective of this survey? 1.2) affiliation ("Public or Private Research Organization/Regulatory Agency/Other Public or Private Organization ") 1.3)What role do you have with respect to the ATC/DDD Classification System in your country? ("researcher/user";

			"regulator/technician"; both)[1]
2)Availability of, and accessibility to, one or more medicinal product dictionary(s)[2] linked to the ATC/DDD index and corresponding DPP	Existence of one or more dictionary[2] of medicinal products linked to the ATC/DDD Classification System Per each available dictionary linked to the ATC/DDD Classification System: - Type of medicinal product listed in the registry - availability of DPPs - Accessibility of such register(s) to the public	This section will allow to understand if one or more dictionary[2] of medicinal products linked to the ACT/DDD system are available in the country and, for each of them, what type of medicinal product are collected, if DPP are also available, and how they are made accessibile to users	2.1)Does any medicinal product dictionarys[2] linked to the ATC/DDD Classification System exist in your country? (yes/no) If answer to question 2.1 is "yes" questions from 2.2 to 2.5 are triggered: 2.2) how many different dictionaries of medicinal products linked to the ATC/DDD Classification System exist in your country?Please, provide a reference name for each available dictionary. #The following questions from 2.3 to2.5 will be associated to the specific registry name and repeated as many times as the number of available dictionaries reported to question 2.2 2.3) what type of medicinal products are listed in the dictionary?(e.g. all nationally approved medicinal products, only reimbursed medicinal products at national/regional level…) 2.4) Are DPP also available in the register? 2.5) Who can access/use this dictionary? (possible answers:"freely accessible on-line (provide link if possible)"/"to anyone upon request"/"to qualified users upon request"(describe)/"upon payment"/"other" If answer to question 2.1 is "no" question 2.6 is triggered 2.6) In which cases and how the ATC/DDD Classification System is used in your country? please, describe (e.g. it is linked only to specific class of medications and for specific research purposes).
3)Governance for implementation and maintenance for dictionary of Medicinal Product linked to the ATC/DDD Classification System	Existence of an organization/institution responsible for the ATC/DDD Classification System implementation Details and available documentation on the governance of the	Information on the governance for the implementation and maintenance of the ATC/DDD Classification System will be collected	#The following questions will be repeated as many times as the number of available dictionaries reported to question 2.2 and associated to the specific dictionary name

	ATC/DDD Classification System implementation		3.1 Can you provide the name of the organization/institution that implement and/or maintain the dictionary 3.2 Is there any accessible documentation that describes the governance of the implementation and maintenance of the reference dictionary? e.g. which organisation is patronising it? who is doing it? what is their expertise? (yes, provide reference/no/No, I can provide a description)
4)Methodological details for ATC/DDD implementation and maintenance	Existence of documentation describing the methodological aspect concerning the implementation and maintenance of the ATC/DDD Classification System Existence of local, non-standard, solution to complement the implementation of the ATC/DDD Classification System Procedures and tools remediate problems like: drugs assigned to wrong ATC, wrong DDD, wrong calculation of DPP, no/incorrect adaptation to new ATC-version, drugs with no linkage to the ATC/DDD Classification System.	Information on the methodology for the implementation and maintenance of the ATC/DDD Classification System will be collected and compared across countries.	#The following questions will be repeated as many times as the number of available dictionaries reported to question 2.2 and associated to the specific dictionary name 4.1 How the calculation of DPP is performed (manually/semi-manually/automatically) 4.2 Is there any document describing this procedure?(yes, provide reference/no/No, I can provide a description) 4.3 How frequently the dictionary is updated? 4.3 Is there any procedure in place for assigning ATC codes to substances that are not addressed by the WHO? (yes/no) 4.4 If yes, is there any document describing this procedure? (yes, provide reference/no/No, I can provide a description) 4.5 Is there any procedure for assigning DDD to ATC codes that were not addressed by the WHO? (yes/no) 4.6 if yes, is there any document describing this procedure?can you provide reference to it? (yes, provide reference/no/No, I can provide a description) 4.7 Is there any quality check/validation process in place with respect to the content of the dictionary?

			4.8 Can you provide details and/or documentation about the quality check/validation process?(yes, provide reference/no/No, I can provide a description)

[1]Role categories= 1)"researcher/user": a scientist who is an expert user of the ATC/DDD Classification System for pharmacoepidemiology/drug utilization research in the country; 2) "regulator/technician": any professional figure involved in the governance and the application of methodologies for the implementation and maintenance of the ATD/DDD system in the country (e.g. regulators, administrative and ICT personnel, terminologists, scientists involved in drug statistics procedures).

[2]Medicinal product dictionary= it is intended as a database containing a dictionary of medicinal products uniquely identified at medicinale product package level that can be linked to the ATC/DDD index and corresponding DDD per package.

3. Limitations

The main limitation of the study will be represented by the possibility of missing nation-specific experts whose knowledge about the implementation and maintenance of the ATC/DDD Classification System might had been relevant for the purposes of the study. This could happen either because we do not identify the all right recipients of the survey or because recipients do not answer to the survey. However, in order to mitigate the risk of missing relevant nation-specific experts, survey recipient will be identified leveraging knowledge and connections of the EuroDURG and ISPE DUR SIG members, and snowballing will be also used to identify further relevant survey recipients (see section 2.2). Moreover , survey will be designed following recommendations for increasing response rate (see section 2.3)

4. Practical implementation and timelines

The execution of the survey is planned to occur in 3 main steps, i.e. 1) survey creation, 2) distribution, 3) analysis of responses and dissemination of results through the publication of a manuscript in a peer-reviewed journal. The three steps and relevant activities are described in Table 2 along with the corresponding expected timeline.

Table 2. Timeline for survey execution

Step	Activity	FEB-JUNE 24	MAY-JUL 24	AUG-SEPT 24	SEPT-OCT 24	OCT-NOV 24	DEC 24 - JAN 25	FEB-APRIL 25
1)Survey Creation	Survey protocol drafting and Ethical approval							
	Survey structure definition and creation in RedCap							
	Pilot survey distribution							
	Survey refinement							

	and update							
2)Distribution	Strategy for distribution							
	collection of emails/contacts							
	Survey distribution							
	Survey collection							
3)Analysis and Manuscript	Analyses of responses							
	Drafting of results and discussion							
	Abstract submission to ICPE 2025							
	Manuscript submission							

5. Ethical considerations

The present survey-based study will be compliant with national and international regulations and laws concerning research involving human participants and the collection and processing of personal data, such as:

- The General Data Protection Regulation (GDPR)
- Directive 2002/58 on Privacy and Electronic Communications.
- UK Data Protection Act 2018

In addition, we will strictly respect the ethical principles expressed in:

- Charter of Fundamental Rights of the European Union (2012)
- European Code of Conduct for Research;
- The Belmont Report (1979)
- Declaration of Helsinki (2013)

This study involves human subjects. Therefore, ethical approval will be requested to the Bioethics Committee of the University of Bologna(22).

In addition, on the basis of specific local rules, ethical approval will also be obtained where requested.

Consent for participation will be required on an informed basis. Such information will be provided both in the invitation email and on the survey landing page. The exact text for the

informed consent is available in the appendix.

The invitation email will provide information on the Data Protection Officer (DPO) of the coordinating center where data will be stored, the Agenzia regionale di sanità della Toscana (ARS), and clearly address the data protection procedures. Informed consent will be given by the individual choosing to participate in the survey by clicking on 'Take the survey'.

In particular, survey participants will receive information on:

- How their personal data will be used;
- Who will have access to their data;
- The voluntary basis of the participation;
- Duration of data retention;
- Right of withdrawal of participation and data at any time;
- Risk and burden of participation;
- Benefits of participation;
- Procedures to be implemented in the case of incidental findings.

Collecting sensitive data is not the purpose of this survey. There will be no commercial exploitation of this research.

5.1 Participant burden & risk

The study poses a small risk of discovering sensitive information on respondents. All steps necessary to minimize the risk of disclosing sensitive information will be undertaken before sending data to others (e.g. personal details like email address and other data that might directly/indirectly reveal sensitive information will be censored) as well as for the dissemination of study results. With this respect, affiliation of respondents will be also reclassified according to standard categories (e.g. university, national medicine agency, governmental research organization)

5.2 Benefits of participation

There are no direct personal benefits of participation in this study. Participants will not receive any financial incentives. Given the nature of the target population of this study, respondents will benefit more broadly from the result of this survey which will contribute to standardization and harmonization of ATC/DDD Classification System implementation and maintenance across countries, finally fostering pharmacoepidemiology and drug utilization

research.

5.3 Data management and privacy

Full documentation, including contact details for the data responsible partner will be made available alongside all data. Data will be maintained and managed in accordance with the FAIR principles guiding scientific data management(23).

Data Storage

Non-anonymised survey responses for both the pilot and the final survey will be gathered and stored on GDPR compliant platform on the server of the Agenzia regionale di sanità della Toscana, Florence, Italy.

In the first instance data gathered via RedCap software will be stored locally at Agenzia regionale di sanità della Toscana and handled for the purposes of data collection / cleaning / analyses.

Data preservation will comply with GDPR regulations. Collected non-anonymised data will be stored for a period of five years following the publication of the relevant manuscript in a peer review journal. It will be the responsibility of the study coordinator, Giuseppe Roberto, to ensure that all non-anonymised data is deleted at that point. Participants will be informed about this in the consent information provided at the survey initiation.

Data Access

Access to collected data will be granted only to researchers participating in this study that will be involved in data analysis. Sensitive data will not be made publicly available. Anonymised data will however be made openly available upon request.

Anonymisation of data

Data will be anonymised according to standard protocols. Any personal identifiers (e.g. email addresses) will be removed and replaced with an anonymous id. Moreover, all steps necessary to minimize the risk of indirectly disclosing sensitive information will be undertaken (e.g. affiliation of respondents will be also reclassified according to standard categories).

Only anonymised data will be used for analysis.

In case of a data breach, affected participants will be contacted and data will be temporarily removed from the compromised storage.

5.4 Expected outputs

The expected output of this study is a scientific article to be disseminated through scientific conferences as well as the peer-review journal Pharmacoepidemiology and Drug Safety.

6. References

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7. Appendices

7.1 Invitation Letter

a) Body of the invitation letter

Dear NAME OF RESEARCHER,

This is an invitation to participate in a survey promoted by the European Drug Utilization Research Group

(EuroDURG) and the Special Interest Group on Drug Utilization of the International Society for Pharmacoepidemiology (SIG DUR ISPE).

A survey was created by a group of colleagues from nine countries across all continents joining the **"Exposure to Medications Measured using the ATC/DDD Classification System" (EMMA) initiative** (Approval n. xxxxx from Ethics Committee of the University of Bologna, Italy), with the aim of gathering country-level information on how the ATC/DDD classification system is implemented (i.e. how medicinal product package dictionaries are linked to the ATC/DDD index) and maintained, and how such registers are made available to users.

The final goal of this initiative is to provide recommendations for fostering the harmonization of the ATC/DDD implementation process and ultimately facilitate the study of medicines use around the globe.

There are no direct personal benefits of participation in this study.

By participation, you will contribute to the collection of nation-level information useful to identify good practices and sources of misalignment across countries with respect to the implementation and maintenance of the ATC/DDD Classification System.

If you decide to contribute this initiative by taking the survey, please note that your participation will remain completely anonymous.

The survey should take no more than 15-20 minutes to be completed.

You are free to decline to answer any question if you do not wish to answer it for any reason, and you can exit the survey at any time.

You can exit the survey at any time without any penalty.

Please, click on the link below to accept/decline the invitation to contribute to this survey:

[link to accept/decline invitation]

In case of major doubts or problems, we kindly ask you to email to emmaproject.atcddd@gmail.com.

We thank you in advance for your kind contribution,

The EMMA project members

b) Content of the [link to accept/decline invitation]

- Yes, I accept the invitation to participate to the survey
  - "Could you suggest another expert in the field that may be interested in contributing to this survey?

    Please note that potential recipients of the survey are scientists using the ATC/DDD Classification System for pharmacoepidemiology/medicine utilization research as well as any other professional figure who may be involved in the governance or methodology applied to its implementation and maintenance (e.g. regulators, administrative and Information and Communication Technologies staff, terminologists, scientists engaged in statistical procedures on medicines).
    Thanks in advance for your collaboration!"

    (FREE TEXT FIELD)

- No, I decline the invitation to participate to the survey
    - I do not have time
    - I am not able to meet the deadline for survey completion
    - I am not available
    - This is not my field of expertise
    - I prefer not to answer
    - Other (free text field)

      - "Could you suggest another expert in the field that may be interested in contributing to this survey?

      Please note that potential recipients of the survey are scientists using the ATC/DDD Classification System for pharmacoepidemiology/medicine utilization research as well as any other professional figure who may be involved in the governance or methodology applied to its implementation and maintenance (e.g. regulators, administrative and Information and Communication Technologies staff, terminologists, scientists engaged in statistical procedures on medicines).
      Thanks in advance for your collaboration!"

      (FREE TEXT FIELD)

7.2 Questionnaire

1) Respondent information	
1.1) What is the country for which you can provide information that is relevant to the objective of this survey?	Opened ended
1.2) Your affiliation	Close ended - Public or Private Research Organization - Regulatory Agency -Other Public or Private Organization
1.3) What role do you have with respect to the ATC/DDD Classification System in your country?[1]	Close ended/open ended[1] - researcher/user - regulator/technician - both the previous

1.4) years of experience with the ATC/DDD (ie.e years since you started using the ATC/DDD classification system in the context of your working activities)	Close ended - less than 1 year - between 1 and 5 years - between 6 and 10 years -more than 10 years
2) Availability of, and accessibility to, a national medicinal product dictionary linked to ATC/DDD Classification System	
2.1) Do any medicinal product dictionaries[2] linked to the ATC/DDD Classification System exist in your country? (yes/no)	Close ended[2] - Yes - No If answer to question 2.1 is "yes" questions from 2.2 to 2.5 are triggered If answer to question 2.1 is "no" question 2.6 is triggered
2.2) How many different medicinal products dictionaries linked to the ATC/DDD Classification System exist in your country? Please, provide a reference name for each available register. #The following questions from 2.3 to2.5 will be associated to the specific registry name and repeated as many times as the number of available dictionaries reported to question 2.2	Open ended - Reference name for Dictionary Number 1 - Reference name for Dictionary Number 2 - Reference name for Dictionary Number X
2.3) what type of medicinal products are listed in the dictionary X? (e.g. all nationally approved medicinal products, only reimbursed medicinal products at national/regional level…)	Open ended/close ended - I don't know - Please describe
2.4) Are DPP also available in the register?	Close ended - Yes - No - I don't know
2.5) Who can access/use this register?	Open ended/close ended - freely accessible on-line (provide link if possible) - anyone upon request - qualified users upon request (please describe is possible) - upon payment - I don't know - Other (please describe if possible)

2.6) In which cases and how the ATC/DDD Classification System is used in your country? please, describe (e.g. it is linked only to specific class of medications and/or for specific research purposes)	Open ended
3) Governance for the implementation and maintenance of the Medicinal product dictionary linked to the ATC/DDD Classification System #questions within this topic will be repeated as many times as the number of available dictionaries reported to question 2.2. and associated to the specific dictionary name	
3.1) Can you provide the nature and name of the organization/institution that implement and/or maintain the dictionary	Close ended/Open ended - Private (Please, possibly provide the name of the organization) - Public (Please, possibly provide the name of the organization) - I don't know
3.2) Is there any accessible documentation that describes the governance of the implementation and maintenance of the reference register? (e.g. which organization is patronizing/sponsoring it? Who is doing it? what is their expertise?)	Close ended/Open ended - yes (please provide reference if possible) - no - No, but I can provide a description (please describe) - I don't know
4) Methodological details for the implementation and maintenance of the Medicinal Product Dictionary linked to the ATC/DDD Classification System #The following questions will be repeated as many times as the number of available registers reported to question 2.2 and associated to the specific registry name #Questions (4.1 and 4.2) do not apply if the answer to point 2.4. is no	
4.1 How is the calculation of DPP performed?	Close ended - manually - semi-manually - automatically - I don't know
4.2 Is there any document describing this procedure?	Close ended/Open ended - yes (please provide reference if possible) - no - No, but I can provide a description (please describe) - I don't know
4.3 How frequently the register is updated?	Open ended/close ended

	- Please describe - I don't know
4.4 Are Historical versions of the dictionary available?	Close ended - Yes - No - I don't know
4.5 Are changes of the ATC/DDD index applied retrospectively to all medicinal products packages in the dictionary and corresponding ATC/DDD/DPP?	Close ended - Yes - No - I don't know
4.6 Is there any procedure in place for assigning ATC codes to substances that are not addressed by the WHO?	Close ended - Yes - No
4.7 If yes, is there any document describing this procedure?	Close ended/Open ended - yes (please provide reference if possible) - no - No, but I can provide a description (please describe) - I don't know
4.8 Is there any procedure for assigning DDD to ATC codes that were not addressed by the WHO?	Close ended - Yes - No
4.9 if yes, is there any document describing this procedure? can you provide reference to it?	Close ended/Open ended - yes (please provide reference if possible) - no - No, but I can provide a description (please describe) - I don't know
4.10 Is there any quality check/validation process in place with respect to the content of the dictionary?	Close ended - Yes - No
4.11 Can you provide details and/or documentation about the quality check/validation process?	Close ended/Open ended - yes (please provide reference if possible) - no - No, but I can provide a

	description (please describe) - I don't know
5) Suggested contacts	
5.1 Can you recommend a contact person that you find appropriate for providing information that can add/complement to the information that you provided?	Open ended

[1]Role categories= 1)"researcher/user": a scientist who is an expert user of the ATC/DDD Classification System for pharmacoepidemiology/drug utilization research in the country; 2) "regulator/technician": any professional figure involved in the governance and the application of methodologies for the implementation and maintenance of the ATC/DDD system in the country (e.g. regulators, administrative and information and communication technology personnel, terminologists, scientists involved in drug statistics procedures).

[2]Medicinal product dictionary= it is intended as a database containing a dictionary of medicinal products uniquely identified at medicinal product package level that can be linked to the ATC/DDD index and corresponding DDD per package.

7.3 Informed consent text

You are invited to participate in a web-based online survey aimed at collecting information on how the ATC/DDD Classification System is implemented, maintained and made available to the public in your country.

This study was endorsed by European Drug Utilization Research Group (EuroDURG) and the Special Interest Group on Drug Utilization Research of the International Society of Pharmacoepidemiology (ISPE SIG DUR). Researchers belonging to these communities are conducting this survey-based study.

The survey should take no more than 15-20 minutes to complete.

Your participation in this survey is voluntary. You may refuse to take part in the research or exit the survey at any time without penalty. You are free to decline to answer any particular question you do not wish to answer for any reason.

If you would like to participate, please click on the 'Take the survey' button found at the bottom of this page.

Your participation in the survey will remain completely anonymous.

By taking the survey you agree to be possibly recontacted by the study investigators in case clarifications are needed.

If you initially decide to participate but change your mind later, you are free to withdraw by sending an email to Giuseppe Roberto, principal investigator (giuseppe.roberto@ars.toscana.it). You do not have to provide us with reasons for the termination of your participation. When you withdraw from the study, all your non-anonymized data will be destroyed. If your data has already been analyzed, the results will be used but the source of the data will not be retrievable.

There are no direct personal benefits of participation in this study. By participation, you will contribute to the collection of nation-level information on how the ATC/DDD Classification System is actually implemented, maintained and made accessible. This will allow us to identify good practice and sources of misalignment across countries and provide recommendations for fostering the harmonization of the process of implementation and maintenance of the ATC/DDD

Classification System, which will ultimately facilitate the study of medicine use around the globe.

The study poses a small risk of discovering sensitive information. Before sharing data to other researchers and/or disseminate study findings, we will take all steps necessary to minimize this risk by masking and/or reclassifying to standard categories any data that might directly or indirectly reveal sensitive information.

Storage and use of the data collected during the study will be in alignment with the data protection procedures contained in the European Union Law, specifically Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation - applicable as of 25 May 2018 in all European Union member states).

All data collected through the online survey will be stored on the server of the Agenzia regionale di sanità della Toscana (ARS). The access to the stored data will be enabled only for researchers participating in this survey-based study. This data will be deleted five years after the final publication of the relevant manuscript.

The ethics approval for conducting interviews was obtained from the bioethical committee of the University of Bologna.

By clicking on 'Take the survey', I indicate that:

-I have read the information provided about the study. I had the opportunity to ask questions and my questions have been sufficiently answered. I have had enough time to decide whether I would like to participate.

-I am aware that participation in the study is voluntary. I also know that I can decide at any moment to not participate or withdraw from the study. I do not have to provide any reasons for not participating or terminating enrolment in the study.

-I give consent to the collection and use of my data as described in the information on this page.

-I give consent to having my anonymized data publicly available. I understand that this means that the anonymized data can be used for research purposes other than the ones described in the information leaflet. I am also aware that this means that my anonymized information may be used in countries outside of Europe and that the regulations for data processing and storage in those countries may not comply with those of the European Union.

-I want to participate in this study.

If you have questions at any time about the study or the procedures, you may contact the principal investigator, Giuseppe Roberto (giuseppe.roberto@ars.toscana.it)

7.4 Privacy Policy

This document describes the privacy policy that all research activities conducted in this work are committed to follow.

Collection, storage and use of the data collected during the online survey will be in alignment with the European Union's General Data Protection Regulation (GDPR).

The ethical approval of the survey was obtained from the bioethics committee of the University of Bologna.

Before taking part in the online survey, all participants will be presented with an email which includes information on the project's purpose, funding, recruiting processes, methodologies, expected risks, beneficiaries of research results, communication of research results and all matters concerning collected data as described in this document.

Consent will be indicated by agreeing to click on the survey link.

All data material will be stored safely on the server of the Agenzia regionale di sanità della Toscana (ARS), a GDPR compliant platform, administered by the study coordinator Giuseppe Roberto All data will be encrypted and stored at on the server of the Agenzia regionale di sanità della Toscana (ARS) for 5 years after the publication of the relevant manuscript on a peer-reviewed journal. The study coordinator, Giuseppe Roberto (giuseppe.roberto@ars.toscana.it), will ensure this data is also destroyed at this point. The findings from the online survey will be analyzed, published and made publicly available. No personal identifiable information will be mentioned or disclosed at any point.

Data preservation will comply with GDPR regulations, and it is the responsibility of the study coordinator, Giuseppe Roberto (giuseppe.roberto@ars.toscana.it), to ensure that sensitive data is secured and deleted in accordance with the GDPR regulations. Each participant in the online survey may at any time demand removal of his/her survey data by a simple request to the coordinator of the study, Giuseppe Roberto (giuseppe.roberto@ars.toscana.it). However, data, which have already been published, cannot be removed.

To promote open science and avoid research waste, anonymized data from the focus group interviews will also be made available upon request to the study coordinator, Giuseppe Roberto (giuseppe.roberto@ars.toscana.it).

The Data Controller is ARS Toscana, located in Florence, Via Pietro Dazzi, 1 - 50141. The Data Protection Officer (DPO) can be contacted at the following email address: dpo@ars.toscana.it, to exercise the rights of access, confirmation, rectification, erasure, restriction, and objection.

For any information and clarification regarding this study or for any needs, you can contact the researcher (giuseppe.roberto@ars.toscana.it), who is available for further information or clarifications.

To exercise your rights, you can contact the Data Controller at the email address: ars@postacert.toscana.it, or by sending an email request to the scientific supervisor of the project, at the email address: giuseppe.roberto@ars.toscana.it.

If the conditions are met, you also have the right to lodge a complaint with the supervisory authority of the state of residence (Art. 77 GDPR), according to the procedures provided for in Article 142 of Legislative Decree no. 196/2003, as amended by Legislative Decree no. 101/2018.