Two initiatives aimed at improving the use of the ATC/DDD methodology in drug utilization research:

the Italian Working Group on DDDs

and

the EMMA project

Giuseppe Roberto, PharmD PhD

Agenzia regionale di sanità della Toscana, Florence - Italy

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Disclosure

I work as a senior pharmacoepidemiology consultant at the Epidemiology unit of ARS Toscana, the Regional Health Agency of Tuscany, Italy, which is a governmental research organization.

ARS Toscana is also involved in drug utilization and pharmacoepidemiological studies that are funded by both public and private organizations.

1) **Introduction**

2) **The Italian working group on DDD**

3) **The EMMA project**

The ATC/DDD classification system in DUR/pharmacoepi

- It represents a widely used global standard for drug utilization research (DUR) and pharmacoepidemiology

- The ATC system allows for classification, grouping and retrieval of active substances

- DDDs provides a standard unit of measure for drug consumption statistics that facilitates evaluation of temporal trends and comparisons across different populations. Also useful for defining duration of prescription/dispensing records

- The implementation of the ATC/DDD classification system against national Medicinal Product Package Dictionaries provides a readily available and extremely powerful standard tool for DUR and pharmcoepi

Issues related to the use of the ATC/DDD methodology in DUR/pharmacoepi:

- **Usage/applicability**

  - DDDs are not available for all substances used in practice!

→ **Ita-DDD-wg**

- **Replicability/comparability of studies:**

  - implementation and maintenance of ATC/DDD index is prone to errors and misalignments

  - lack of ATC/DDD-specific reporting recommendations/checklist

→ **EMMA project**

1) Introduction

2) **The Italian working group on DDD**

3) The EMMA project

The Italian Working Group on DDDs (Ita-DDD-wg)

- **Composition:** inter-society initiative of 20 researchers from the Italian Association of Epidemiology and the Italian Society of Pharmacology

- **Aim:** to develop a transparent and reproducible methodology to assign missing DDD

- **Motivation**: improve/facilitate the usage and applicability of the ATC/DDD methodology in DUR and pharmacoepidemiology

The first product of the Ita-DDD-wg

Assignment of Defined Daily Doses (DDD) not yet established in the ATC/DDD system by WHO

ATC L - Antineoplastics and immunomodulating agents

A DDD was assigned to 44 ATC codes of anti-cancer drugs and shared with the WHO-CC

By the Italian Working Group for the assignment of missing DDDs

Giuseppe Roberto, Giulia Hyeraci, Anna Girardi, Rosa Gini – Agenzia Regionale di Sanità della Toscana, Firenze
Gianluca Trifirò, Ylenia Ingrasciotta, Valentina Ientile – Università di Verona
Elisabetta Poluzzi – Università di Bologna
Giampiero Mazzaglia, Ippazio Cosimo Antonazzo – Università degli Studi di Milano-Bicocca
Manuela Casula, Elena Tragni – Università degli studi di Milano
Olivia Leoni, Arianna Mazzone, Michele Ercolanoni, Martina Zanforlini – Regione Lombardia
Ursula Kirchmayer, Valeria Belleudi, Marco Finocchietti– Dipartimento di Epidemiologia del Lazio
Francesco Barone Adesi – Università del Piemonte Orientale

3. List of ATC codes and the corresponding DDDs assigned by the Ita-DDD-wg (4)

ATC V	ATC V description	Route of administration	Reference indication of use	Reference posology	Assignment criteria	DDD calculation	DDD	Unit of measure
L01AB02	TREOSULFAN	Parenteral	Allogeneic haematopoietic stem cell transplantation	14g/m^2 for 3 consecutive days	recommended dose*reference BSA	14g/m^2*1.8 m^2	25	g
L01BB04	CLADRIBINE	Parenteral	Hairy cell leukaemia	0.09mg/kg/die (single 7-day treatment cycle)	recommended dose*reference weight/treatment cycle	0.09 mg/kg*70kg/die	6.3	mg
L01BC08	DECITABINE	Parenteral	Acute myeloid leukaemia	20mg/m^2 for 5 consecutive days per treatment cycle of 28 days	recommended dose*reference BSA/treatment cycles	[(20 mg/m^2*1.8 m^2)*5 days]/28 days	6	mg
L01BC52	FLUOROURACIL, COMBINATIONS	Transdermal	Hyperkeratotic actinic keratosis	application on up to 25cm^2 of skin surface daily	assumed mean amount of pharmaceutical product	-	2	ml
L01BC59	TRIFLURIDINE, COMBINATIONS	Oral	Colorectal cancer	35mg/m^2/dose twice daily on Days 1 to 5 and Days 8 to 12 of	recommended dose*reference BSA/treatment cycle	[(35 mg/m^2 *1.8 m^2*2)*10days]/28days	22	mg

Methods for DDD assignment

1) Main indication according to available evidence and/or Ita-DDD-wg knowledge

2) Posology from Summary of product characteristics (SmPC)

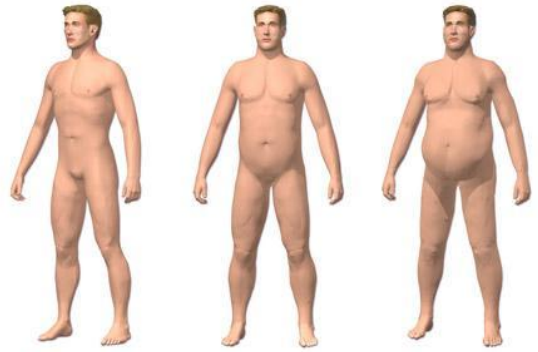
3) Criteria for DDD calculation and assignment from WHO Guidelines

4) Ad hoc criteria defined by the Ita-DDD-wg for:
   a) treatment dosing based on weight and/or body surface
   b) treatment cycles
   c) topical formulations

Treatment dosing based on weight or body surface area (BSA)

Ad hoc criteria:

1) **Recommended dose*reference weight**
(reference weight=70kg according to Guidelines)



or

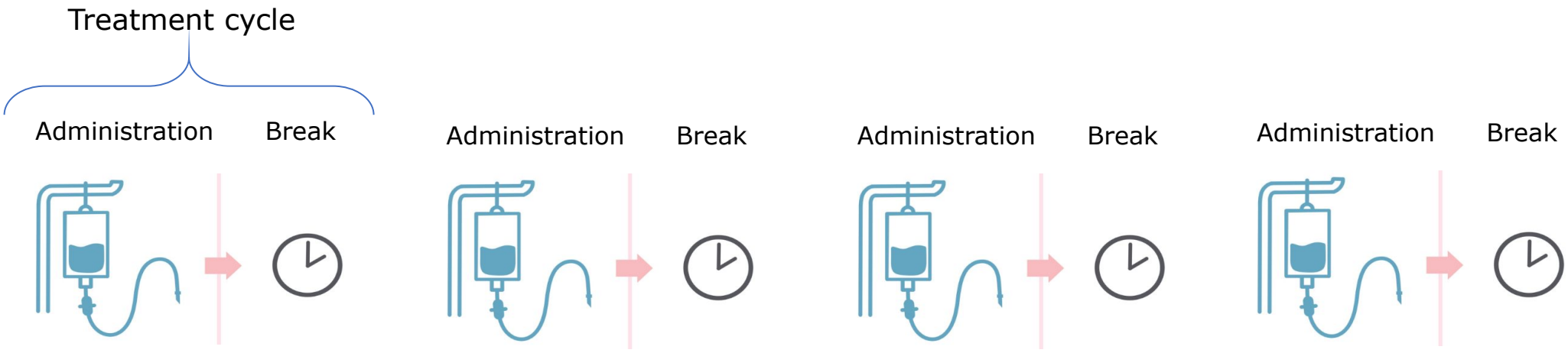
2) **Recommended dose*reference BSA**
(Reference BSA=1.82 according to Ita-DDD-wg, i.e. using Dubois[1] formula, 70kg of weight and 1.70m of height)

Dubois D, Dubois EF. A formula to estimate the approximate surface area if height and weight be known. *Arch Intern Med*. 1916; 17:863-871

Drugs administered in cycles

Ad hoc criteria:

- **Recommended dose/treatment cycle**
  (The recommended dose was divided by days of duration of one treatment cycle)



Topical product in multi-dose containers

Ad hoc criteria:

- **Mean daily amount of pharmaceutical product** (approximation of the mean volume or mass of pharmaceutical product needed)

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AIE farmacoepi

Ita-DDD-wg contribution to the ATC/DDD methodology

- DDD calculation criteria potentially applicable to other antineoplastic drugs as well as to drugs from other classes
- Proposed a transparent and reproducible approach for reporting on DDD assignment criteria
- The proposed reporting approach can reduce the risk of misuse of DDD and facilitate interpretation of results

Upcoming activities of Ita-DDD-wg

- Ophthalmological and otological medications (ATC S)

- Results will be shared with WHO-CC

1) Introduction

2) The Italian working group on DDD

3) **The EMMA project**

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EuroDURG
European Drug Utilization Research Group

EMMA project:

Exposure to Medicines Measured using the ATC/DDD classification system

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Project members

- 33 researchers from over 20 different institutions belonging to the EuroDURG and DUR Special Interest Group of the International Society for Pharmacoepidemiology (ISPE)

Australia/Asia/Pacific:

- Gillian Caughey

Europe/Africa:

- Giuseppe Roberto, Rosa Gini, Elisabetta Poluzzi, Ursula Kirchmayer, Robert Vander Stichele, Björn Wettermark, Ilse Truter, Carlos E. Durán, Hege Salvesen Blix, Anna Girardi, Giulia Hyeraci, Judit Riera, Oliver Scholle

North America:

- Mina Tadrous, Jessica Riad, Macarius Donneyong

South America:

- Luciane Cruz Lopes, Danielle Maria S. Santos, Martín Cañás, Juan Roldan, Lysien Ivana Zambrano, Juan Carlos Sánchez Salgado, Maite Inthamoussu, Noelia Speranza, Karla Vizcarra, Jose Salvador Carrillo, Svetlana V. Doubova, Martin A. Urtasun, Gustavo H. Marin, Ana C. Figueiredo Modesto, Mariana Del Grossi

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Background

- Implementation and maintenance of the ATC/DDD index might be prone to errors or misalignments in the application of WHO guidelines

- Divergent ATC/DDD versions, divergent assignment of ATC codes and/or DDDs, use of unofficial/national DDDs were already documented as methodological issues hampering the collection of comparable data on drug use across Europe

Aims of the EMMA Project:

1. To collect nation-level information on the implementation and maintenance of the ATC/DDD classification system, as well as on the accessibility of the relevant documentation and resulting Medicinal Product Package Dictionaries linked to the ATC/DDD index

On-line survey

2. To describe how the use ATC/DDD methodology is reported in recently published drug utilization/pharmacoepi studies

3. To develop recommendations for the design and creation of a prototype online application for the certified calculation of number of DDDs per package

1) EMMA survey

Objectives:

- to collect nation-level information on the implementation and maintenance of the ATC/DDD classification system

- to highlight good practices and possible sources of misalignment across countries with respect to methods and governance, and accessibility to both reference documentation and corresponding Medicinal Product Package Dictionaries linked to the ATC/DDD index

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Topics of the survey

1. Respondent information
2. Availability of, and accessibility to, Medicinal Product Package Dictionaries linked to ATC/DDD Classification System
3. Governance for the implementation and maintenance
4. Methodological aspects

A cross-national survey on the implementation and maintenance of the ATC/DDD Classification System

Respondent information

What is the country for which you can provide information?

If you do not want to answer, please write "I prefer not to answer".

Please note that if you do not answer this question any subsequent answers will not be considered valid for the purpose of this survey.

* must provide value

Your affiliation

* must provide value

What role do you have with respect to the ATC/DDD Classification System in your country?

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/data holder/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, data holder, administrative and information and communication technology personnel, terminologists, scientists involved in drug statistics procedures)

* must provide value

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

To ensure consistency at national level, WHO guidelines recommends that one unique national center should be responsible for implementing and maintaining a reference medicinal product package dictionary linked to the ATC, or ATC/DDDs, index

Is there in your country a national center responsible for implementing and maintaining a reference medicinal product package dictionary linked to the ATC, or ATC/DDDs, index?

A medicinal product package dictionary is a database containing a list of medicinal products uniquely identified at the package level, which can be linked to the ATC/DDD index and the corresponding DDD per package.

* must provide value

Yes

Is there any medicinal product dictionary linked to the ATC, or ATC/DDDs, index available in your country?

It might be possible that two or more medicinal product dictionaries linked to the ATC/DDD index are available in the same country. This might occur if such registries are created and/or maintained independently from each other by distinct organizations, if the registries respectively concern different classes of medications (e.g. only prescription drugs rather than any reimbursed by the NHS, medicinal products corresponding to the WHO Essencial Medicine List only) possibly serving as the reference for distinct geographic/administrative areas of relevance (regional/national).

* must provide value

Yes, at least 1 dictionary does exist

Governance for the implementation and maintenance of the medicinal product dictionary linked to the ATC/DDD Classification System

Dictionary test

Can you provide the nature and name of the organization/institution that implemented and/or currently maintains the dictionary?

* must provide value

Private

Please, possibly provide the name of the organization

Is the personnel working in the responsible organization specifically trained/expert for implementing and maintaining the dictionary?

* must provide value

I don't know

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?)

* must provide value

Yes

Please provide reference if possible

How is the number of DDDs per medicinal product package calculated?

* must provide value

Semi-manually

Are DDD assigned also to those ATC codes for which no DDD is available in the ATC/DDD index?

* must provide value

Yes

Is there any mean to distinguish the DDDs assigned locally (i.e. that are not available in the ATC/DDD index), and the corresponding number of DDDs per package,from those DDDs that are available in the ATC/DDD index (e.g. they are flagged accordingly or recorded in distinct columns of the data base)?

* must provide value

No

Is there any accessible document describing the procedures for the calculation of the number of DDD per package and/or the assignment of DDD that are not available in the ATC/DDD index?

* must provide value

Yes

Please, provide reference if possible

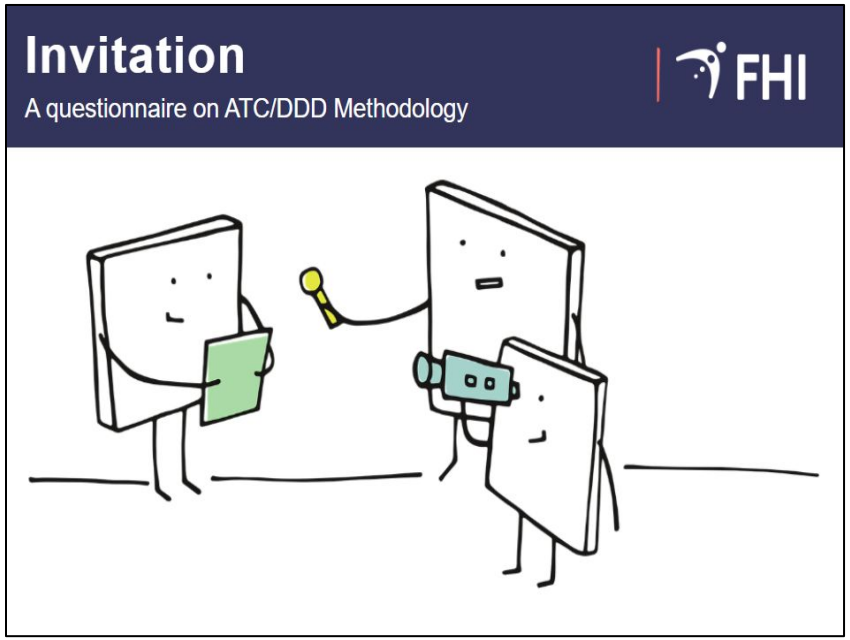
Expand

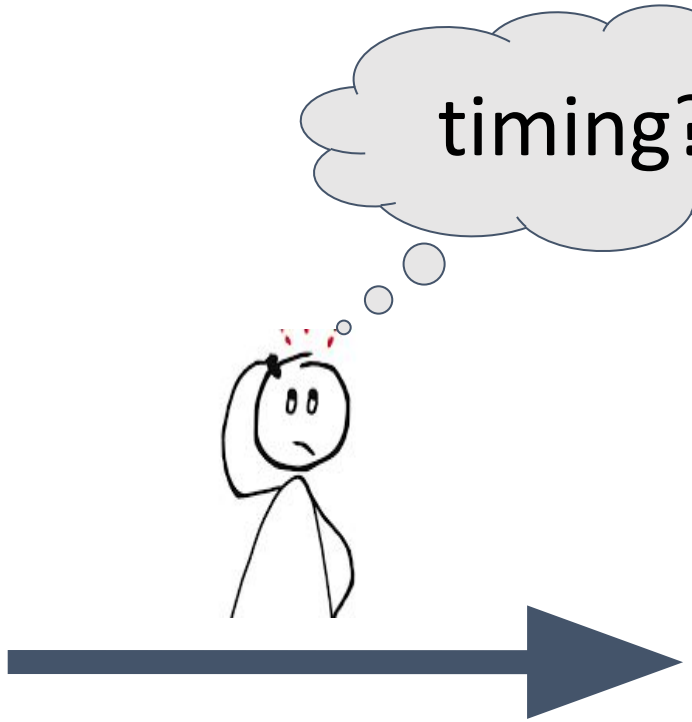
How frequently the medicinal product package dictionary is updated?

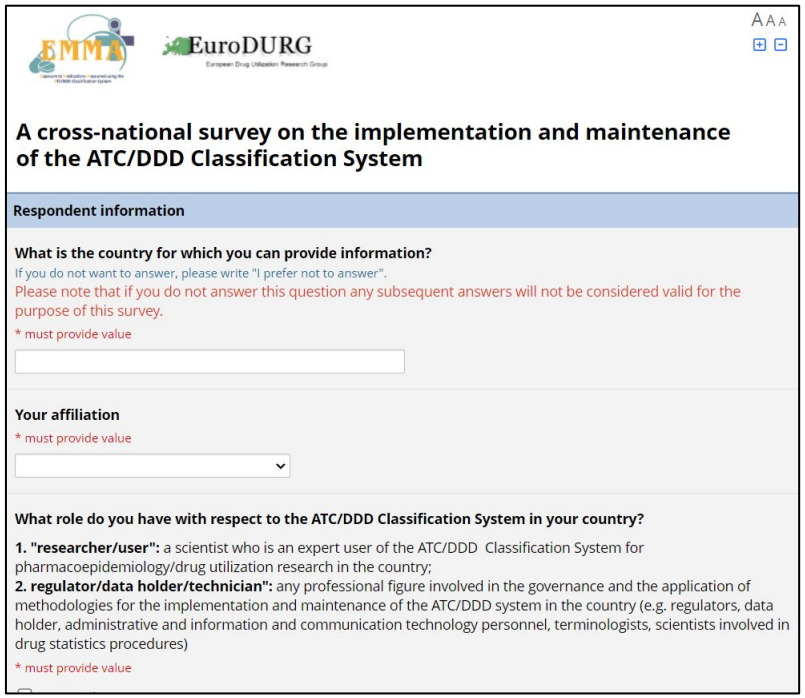
If you do not want to answer, please write "I prefer not to answer"
If you do not, please write "I don't know".

* must provide value

The EMMA survey will collect complementary information with respect to the WHO Questionnaire!!!







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Current Status

- Survey pilot phase will be completed in November

- Distribution list under development
  (*Any input/contribution is welcome!*)

- Start of survey distribution TBD

2) EMMA scoping review

Objectives:

- To document how the use ATC/DDD methodology is reported in drug utilization/pharmacoepi studies published from 2019 to current

- to create expert-based ATC/DDD-specific reporting recommendations and checklist leveraging results from scoping review and survey

Current Status and future development

- Scoping review protocol published in August on OSF repository (https://osf.io/b9n8q/)

- screening of literature search results ongoing

- Reporting recommendations/checklist will be drafted and feedback from other interested party will be sought (e.g. WHO CC)

3) EMMA recommendation on DDD per package calculator

Objectives:

To develop recommendations for the design and creation of a prototype online application for the certified calculation of number of DDDs per package

Current Status

- Kick-off expected by the end of the 2024

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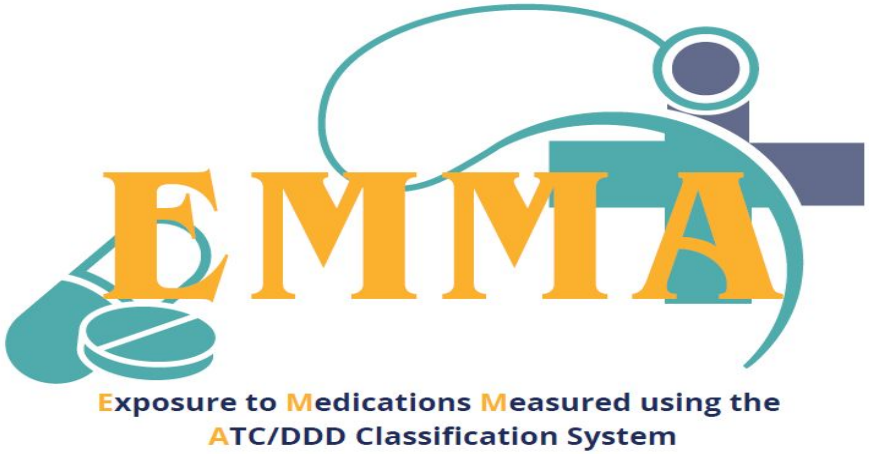
- Previous initiatives and available resources will be leveraged

- Input data compliant with ISO/CEN standards for medicinal products identification

- API of the WHO ATC/DDD index website for the most updated ATC/DDD index

- The R function CreateDoT from the IMI-ConcePTION project for DDDs per package calculation (https://github.com/IMI-ConcePTION/CreateDoT/wiki)



For any information, feedback or input: *giuseppe.roberto@ars.toscana.it*