

## EAHP Academy Seminars 2018



An ACPE application based activity

### Therapeutic drug monitoring as a tool for therapy optimisation

#### About Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) involves the measurement and interpretation of drug concentrations in order to individualise therapy. The indications for TDM include efficacy, compliance, monitoring drug-drug interactions, toxicity avoidance, guiding withdrawal of therapy, and drug should satisfy certain criteria to be suitable for TDM (narrow target range, significant pharmacokinetic variability, a reasonable relationship between plasma concentrations and clinical effects, established target concentration range, availability of cost-effective drug assay). By combining knowledge of pharmaceuticals, pharmacokinetics, and pharmacodynamics, TDM enables the optimisation of drug therapy. Attention must be paid to the timing of blood sampling, the type of biological matrix, the measurement techniques, and the interpretation of results. To accurately interpret measured concentrations, it is important the request form contains all relevant information: time sample collected, time dose given, dosage regimen (dose, duration, dosage form), patient demographics (age/gender), other medications, relevant co-morbidities (e.g. renal/liver disease), indications for testing (e.g. toxicity, non-compliance). Drug concentrations should be interpreted in the context of the clinical data and hospital pharmacists need to be aware of many factors that influence measured concentrations. Performing TDM requires a multidisciplinary approach and collaboration by a TDM team, comprised of clinicians, nurses, hospital/clinical pharmacists.

#### The Educational Need

Topics of EAHP events are fixed both in a **top-down** manner by the Scientific Committee and directly arising from the fields the members daily are moving in, such as:

- Politics
- Practice
- Education
- Current research and development
- New professional opportunities

- New technology
- New medicines
- New methodologies
- New treatments
- Research and development

and in a **bottom-up** manner by

- Proposals from members
- Surveys (544 responses at the 2014 Congress' Cyber Café) / Questionnaires (every five years)
- National associations based on their national strategies
- Focus groups
- Joint commissions
- Mandated members of the Scientific Committee.

Generally, topics will be approved by the EAHP Board. Educational need and gaps between best and current practice and actual versus desired skills respectively can be easily screened by the Scientific Committee from

- EC resolutions
- EAHP surveys (by Survey Monkey® or Adobe Acrobat® form generator)
- FIP statements
- Current agenda of the Board
- The Scientific Committee Meetings
- The General Assembly
- Evaluation of submitted abstracts for poster or oral presentation
- Past congresses' evaluations
- Existing data such as surveys, questionnaires, et cetera

The aim of this Academy Seminar is to provide tools which improve the position of the hospital pharmacist in Research & Development activities adapted to the own institution's environment.

### **Target audience**

Delegates nominated by their national associations should fulfil specific requirements such as

- be hospital pharmacists recommended by each country's national association president;
- be hospital pharmacists who wish to be involved in the planning and implementing therapeutic drug monitoring in their hospital;
- be fluent in English;
- attend all seminar sessions;
- complete seminar evaluation form;
- give presentation and/or demonstrate knowledge gained during workshops and seminar concluding session;
- must be able to accurately disseminate the knowledge obtained during the academy seminar within their country via seminars or workshops and provide documentation that dissemination was done (i.e. national workshop agendas). The national associations then need to report back on how this was accomplished to the EAHP via the country report which is presented each year during the EAHP General assembly.

## **Links to the EAHP mission & goals and to the European Statements of Hospital Pharmacy**

The main EAHP goal covered by the Academy Seminar on Therapeutic drug monitoring as a tool for therapy optimisation is to promote role of hospital pharmacists in therapy optimisation by providing TDM services.

In addition to the European Statements of Hospital Pharmacy, the need is also arising from hospital pharmacy practice, since the topic “Therapeutic drug monitoring” has been proposed in the Cyber Café Needs Assessment Survey at the EAHP Congress and from the EAHP Scientific Committee’s experience when evaluating submitted abstracts.

Educational needs are linked to the European Statements of Hospital Pharmacy, Section 4 (Clinical Pharmacy Services), items 4.1, 4.3, 4.8 and Section 5 (Patient Safety and Quality Assurance), item 5.1 , 5.2, 5.6.

### **Assessment of Learning Success**

To evaluate the learning success as requested by ACPE and as defined by teaching goals and learning objectives, a Survey Monkey® driven online questionnaire will be used. This form can be completed online on day 2 after the Academy Seminar, et cetera. The link will be communicated to the delegates. A participation certificate will be delivered by link after anonymous submission of the completed questionnaire.

## **Contents and Learning Objectives of the lectures**

The Academy Seminar and Workshops show a main track from a general overview to national clinical implications. The focus is put and centred on the patient and on processes.

To clarify terms and obtain a commonality of understanding, some definitions might be outlined as far as they are needed to exclude misunderstandings. However, a broad discussion and philosophy on the terms is excluded.

### **Learning objectives of Academic Seminar**

Participants will be able to:

- recognise characteristics of drugs that make them good candidates for TDM
- describe appropriate indications for TDM
- understand the factors that may affect measured concentrations
- list and discuss the importance of information needed when requesting drug concentration
- interpret measured drug concentrations
- adjust dose based on TDM

### **Link to Hospital Pharmacy Statements**

The following chapters of the Hospital Pharmacy Statements are applied within this topic: Section 4 (Clinical Pharmacy Services), items 4.1, 4.3, 4.8 and Section 5 (Patient Safety and Quality Assurance), item 5.1, 5.2, 5.6.

## Concept of Therapeutic drug monitoring (TDM)

*Prof Dr Branislava Miljkovi? [1], Faculty of Pharmacy, University of Belgrade, Serbia*

### Linked to EAHP Statements

- Section 4, Statement 4.1, 4.3, 4.8
- Section 5, Statement 5.1

### Abstract

The main goal of TDM service is to ensure clinical interpretation of measured drug concentrations in order to optimise drug therapy. The important components of TDM process are: the decision to request a drug measurement, the biological sample, time of sampling, laboratory measurement, clinical interpretation and dose adjustment if needed. The common drug characteristics for TDM include: an established relationship between drug concentrations and therapeutic response and/or toxicity, narrow therapeutic index drugs, large individual pharmacokinetic variability, saturable pharmacokinetics etc. The time of sampling is important as the drug concentration changes during the dosing interval. Measured drug concentrations need to be interpreted in the context of the clinical response, the demographics and clinical status of the individual patient, the used dosage regimen, and the pharmacokinetic characteristics of the drug.

### Learning objectives

At the end of this session, participants will be able to:

- apply basic concept of clinical pharmacokinetics to TDM;
- understand indications for TDM;
- understand the importance of time sampling;
- understand factors that might affect drug concentrations.

### Educational need addressed

Knowledge of clinical pharmacokinetics is necessary to apply its principles to individualised drug therapy.

**Keywords:** clinical pharmacokinetics, pharmacokinetic parameters, pharmacokinetic variability, saturable pharmacokinetics.

## Practical consideration to TDM

*Prof Dr Azucena Aldaz Pastor [2], Clínica Universidad de Navarra, Spain*

### Linked to EAHP Statements

- Section 4, Statement 4.1, 4.3, 4.8
- Section 5, Statement 5.1

### Abstract

Therapeutic drug monitoring aims to achieve the greatest therapeutic benefit in a specific

patient, achieving the maximum possible effectiveness with the minimum incidence of adverse effects. This process requires not only pharmacokinetic, pharmacodynamic and analytical knowledge, but also the clinical skills needed to make decisions. Sometimes different conditions such as co-morbidities, acute pathophysiological changes, etc., may direct the dosage recommendation in an unusual direction, placing the concentrations outside the traditional therapeutic range. This is usually more frequent in pediatric epileptic patients.

During the last years, another discipline of pharmacology, pharmacogenomics, has arisen in the posology optimisation. However, based on the available evidence, it is convenient to differentiate between pharmacodynamic genes and pharmacokinetic genes in order to objectively and efficiently use this new tool.

### **Learning objectives**

At the end of this session, participants will be able to:

- describe analytical needs for therapeutic drug monitoring;
- understand the importance of pharmacogenomics biomarkers;
- understand the importance of genetic factors in the response to drugs.

### **Educational need addressed**

Understanding the practical consideration to therapeutic drug monitoring is needed for interpretation of measured drug concentration.

**Keywords:** therapeutic range, analytical methods, dry blood spot, pharmacogenomics.

### **Population pharmacokinetic analysis of TDM in optimising therapy**

*Prof Dr Kees Neef <sup>[3]</sup>, EAHP Director of Education, Science & Research, Maastricht University Medical Center+, The Netherlands*

### **Linked to EAHP Statements**

Section 4, Statement 4.1, 4.3, 4.8

Section 5, Statement 5.1, 5.2, 5.6

### **Abstract**

#### Estimation methods

In the field of pharmacokinetic modelling the calculation of PK-parameters has changed a lot. Classical pharmacokinetics like the calculation of a distribution volume or half-life using logarithms and standard deviations was used from the beginning of PK modeling. Later the methodology changed towards fitting a pharmacokinetic model to the drug concentrations using linear regression on logarithms of the serum levels, non-linear regression evaluating to likelihood estimation. Finally, when computers became available the Bayesian estimation took over the preferred calculation method. The disadvantages of this linear regression method will be shown shortly.

#### Bayesian estimation

Thomas Bayes, a reverend from the 18<sup>th</sup> century, wrote several essays toward solving a problem in the doctrine of changes (1783). The most important property of this method was the inclusion of all prior information to be used in calculation of the posterior.

### Population models

Population pharmacokinetics is used to obtain a description of the pharmacokinetic behavior of a drug in a population. The description requires a pharmacokinetic model and a statistical model.

The goal of population PK is to characterize the PK of a particular drug in a specific patient, to study the influence of patient characteristics on PK and to use it in MAP Bayesian parameter estimation for dose adjustment in the individual patient. (TDM)

As model parameters can be considered the mean value, the standard deviation, the covariance between parameters and the assessment of covariates.

The characteristics of the data (measurements) are important for the choice of a particular method to estimate the population model (sparse or rich data). The methods that are used are naïve pooling, standard two stage, iterative two stage Bayesian, mixed-effect modelling, non-parametric methods.

An important covariate is the renal function. Creatinine clearance therefore is discussed in relation to the calculation of the glomerular filtration rate. Other covariates are body weight and the assay error pattern.

The process of adaptive control will be explained.

### Inter and intra individual variability

The pharmacokinetic parameters differ from individual to individual. This inter individual variability must be taken into account when the PK parameters are calculated. This can be the result of variability in dose and times. The same holds true for the intra individual variability. Examples are body weight and renal function.

### **Learning objectives**

At the end of this session, participants will be able to:

- describe a pharmacokinetic model for a drug using terms of Volume of distribution, elimination rate constant, renal clearance;
- explain the error and residual error in the used population model.

### **Educational need addressed**

Individualised therapy does need knowledge of both patient and drug related properties. Therapeutic Drug Monitoring opens the possibility to an individualised therapy. Knowledge of basic pharmacokinetic and pharmacodynamic properties of the drug is mandatory to apply this type of pharmacotherapy.

**Keywords:** PK-PD modelling, population pharmacokinetics, therapeutic drug monitoring.

## **TDM and dose optimisation of antibiotics and antifungals**

*Daniel Touw [4], University Medical Center Groningen, The Netherlands*

### **Linked to EAHP Statements**

- Section 4, Statement 4.1, 4.3, 4.8
- Section 5, Statement 5.1, 5.2, 5.6

### **Abstract**

Precision Medicine is rapidly changing modern medicine. In the near future most pharmacotherapy for individual patients will be driven by a combination of phenotyping, genotyping and sophisticated clinical use of pharmacokinetic/pharmacodynamic modeling, especially in patients with bacterial, fungal and other infections.

Only little is presently known about the pharmacokinetic/pharmacodynamic behavior of antibacterial and antifungal drugs. Too low systemic exposure to the drugs will lead to lack of efficacy and the emergence of multiple drug resistant strains. Too high systemic exposure may lead to toxicity and unnecessary costs. Knowledge on pharmacokinetics, pharmacodynamics and its interrelationship and how to translate population values for pharmacokinetics into pharmacokinetics in an individual patient may therefore be of great help in the treatment of the individual patient.

### **Learning objectives**

At the end of this session, participants will be able to:

- describe the pharmacodynamic properties of beta lactam antibiotics;
- describe the pharmacodynamic properties of aminoglycoside antibiotics;
- describe the pharmacodynamic properties of the fluoroquinolone antibiotics.

### **Educational need addressed**

Hospital pharmacists need knowledge and understanding of dose optimisation of antibiotics and antifungals.

**Keywords:** medicines optimisation, phenotyping, modeling, antibiotics, antifungals.

## **TDM and dose optimisation of antiepileptic and antipsychotic drugs**

*Prof Dr Christoph Hiemke [5], University Medical Center Mainz, Germany*

### **Linked to EAHP Statements**

- Section 4, Statement 4.1, 4.3, 4.8

- Section 5, Statement 5.1, 5.2, 5.6

### Abstract

Therapeutic drug monitoring (TDM) uses drug concentrations in body fluids, mostly blood, to optimise pharmacotherapies of individual patients. Historically, the primary aim of TDM was measurement of drug concentrations in blood to identify if patients exhibit drug concentrations within or outside the so-called therapeutic reference range. In psychiatry, TDM is long established and became obligatory to supervise medication with lithium, tricyclic antidepressants or clozapine. During the last 20 years knowledge on pharmacokinetic properties of the multiple psychoactive drugs increased markedly, especially substrate, inhibitor and inducer properties of cytochrome P450 enzymes, the major enzymes involved in the elimination of drugs, were identified. It is thus possible to explain reasons underlying abnormal drug concentrations and use the information for patients care in every day practice. In 2004, the task force of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) issued guidelines on TDM in psychiatry. These guidelines were markedly extended and updated in 2011 and now again in 2018. An overview on primarily theoretical aspects addressed in the guideline will be given such as pharmacokinetics and pharmacogenetics of psychoactive drugs, relations between drug concentrations and clinical effects, definition of reference ranges and actual validity of these parameters.

### Learning objectives

At the end of this session, participants will be able to:

- explain why and how TDM should be used in psychiatry and neurology;
- differentiate between therapeutic and dose related reference ranges;
- explain how genotyping may be combined with TDM;
- use TDM for identification of pharmacokinetic abnormalities.

### Educational need addressed

Hospital pharmacists need knowledge and understanding of dose optimisation of antiepileptic and antipsychotic drugs.

**Keywords:** dose optimisation, individual patient, antiepileptics, antipsychotics.

### **TDM and dose optimisation of immunosuppressive and oncolytic agents**

*Dr Erik van Maarseveen <sup>[6]</sup>, University Medical Center Utrecht, The Netherlands*

### Linked to EAHP Statements

- Section 4, Statement 4.1, 4.3, 4.8
- Section 5, Statement 5.1, 5.2, 5.6

### Abstract

Immunosuppressant drugs have contributed significantly to the success of organ

transplantation. Therapeutic drug monitoring (TDM) is an integral part of transplant protocols. Immunosuppressants require TDM because of their narrow therapeutic index and significant variability in blood concentrations between individuals. The variability in blood concentrations can be because of factors like drug-nutrient interactions, gender influence and polymorphism. Drug monitoring is widely practiced especially for cyclosporine, tacrolimus, sirolimus and mycophenolic acid. Next to TDM in transplantation, there is also substantial evidence for immunosuppressive agents monitoring in other diseases. In contrast, the routine use of TDM in oncology is limited to measurement of plasma methotrexate concentrations after high-dose methotrexate therapy at present. The lack of a more widespread application of TDM in oncology has been due to deficiencies in knowledge about the clinical pharmacology of antineoplastic agents and to factors specific to the chemotherapy of neoplasms. Despite these challenges, there are many areas in oncology where the use of TDM can prove of benefit. As many of these agents have a relatively small therapeutic window compared to other drug classes.

### Learning objectives

At the end of this session, participants will be able to:

- understand basic clinical pharmacokinetics of oncolytics and immunosuppressants;
- comprehend the rationale for TDM of oncolytics and immunosuppressants;

### Educational need addressed

Hospital pharmacists need knowledge and understanding of dose optimisation of immunosuppressive and oncolytic drugs.

**Keywords:** dose optimisation, individual patient, immunosuppressants, antineoplastic agents.

## An Overview of Therapeutic Drug Monitoring Software

*Nieko Punt [7], Medimatics, Maastricht, The Netherlands*

### Linked to EAHP Statements

- Section 4, Statement 4.1, 4.3, 4.8
- Section 5, Statement 5.1, 5.2, 5.6

### Abstract

Model informed therapeutic drug monitoring requires complex algorithms and large amounts of data (medication history, patient data, etc.) to be processed. In order to achieve high service throughput rates and minimize the risk of mistakes, the use of computer software tools for supporting the TDM process has become inevitable. The quality of a TDM service is highly dependent on an optimal organization of the key service components process, people and tools. In this triangle tools will enhance efficiency but not effectiveness of the TDM service. In the past many academic research efforts yielded tools that could be used for TDM (the “long list”). Tools were scored against several criteria among which the user interface, database,

algorithms and drug population models. In practice most of these academic tools are not fit for routine and reliable use in a hospital IT environment. Currently 3 software TDM tools qualify as serious candidates for supporting the TDM process: InsightRX, DoseMeRx and MwPharm++ (the short list).

### **Learning objectives**

At the end of this session, participants will be able to:

- understand that TDM software tools affect efficiency not effectiveness;
- understand the interaction between TDM processes, people and tools;
- gain insight in how software tools support the TDM process cycle;
- understand the key components of TDM software tools;
- evaluate TDM software tools current available on the market (long/short list).

### **Educational need addressed**

Hospital pharmacists need to understand how TDM software tools support TDM process cycle.

**Keywords:** TDM service, software, InsightRX, DoseMeRx, MwPharm++

## **Contents and Learning Objectives of the workshops**

### **Link to Hospital Pharmacy Statements**

The following chapters of the Hospital Pharmacy Statements are applied within this topic: Section 4 (Clinical Pharmacy Services), items 4.1, 4.3, 4.8 and Section 5 (Patient Safety and Quality Assurance), item 5.1.

### **Learning objectives**

At the end of these workshops, participants will be able to:

- assess the need for dose adjustment;
- adjust the dose of drugs based on the results of TDM;
- interpret measured drug concentration;
- develop a Plan for therapeutic drug monitoring;
- provide TDM service.

### **Educational need addressed**

Hospital pharmacists need to understand the interpretation of measured drug concentration and the need for dose optimisation of antibiotics, antifungals, antiepileptics antipsychotics, immunosuppressants, oncolytic drugs.

The contents of the workshops are as follows:

**“Clinical cases on dose adjustments based on TDM of antibiotics and antifungals”**

*Daniel Touw [4], University Medical Center Groningen, The Netherlands*

## Linked to EAHP Statements

- Section 4, Statement 4.1, 4.3, 4.8
- Section 5, Statement 5.1

### Abstract

The workshop aims at providing information about the pharmacodynamics of beta lactam antibiotics, aminoglycosides and the fluoroquinolones. Besides the pharmacodynamics of the azole antifungal drugs will be discussed.

In addition, population pharmacokinetic modelling will be discussed and how to estimate individual pharmacokinetic values from population pharmacokinetic data.

### Learning objectives

At the end of these workshops, participants will be able to:

- know how population pharmacokinetic models are developed;
- know how population pharmacokinetic values are calculated into individual values.

### Educational need addressed

Hospital pharmacists need to understand how to optimise the dose of beta lactam antibiotics, aminoglycosides, fluoroquinolones and azole antifungal drugs to the individual patients' needs.

**Keywords:** beta lactam antibiotics, aminoglycosides, fluoroquinolones, azole antifungal drugs.

**“Clinical cases on dose adjustments based on TDM of antiepileptic and antipsychotic drugs”**

*Prof Dr Christoph Hiemke [5], University Medical Center Mainz, Germany*

## Linked to EAHP Statements

- Section 4, Statement 4.1, 4.3, 4.8
- Section 5, Statement 5.1

### Abstract

Many problems such as non-response, poor adherence or pharmacokinetic interactions with clinical consequences and adverse effects (pharmacovigilance) are well known in patients under neuropsychiatric medication. Therapeutic drug monitoring and pharmacogenetic tests are tools to optimise drug therapies individually in routine clinical care. How to use TDM alone and in combination with pharmacogenetic tests will be trained. Case vignettes on patients exposed to neuropsychiatric drugs will be presented to understand how to do interpretation

and how to use the AGNP guidelines for TDM in neuropsychopharmacology. For training, participants have to analyze the cases in small groups (2 - 3 participants, aided by the course director on request) during a limited period of time during the course. The participants will then present and interpret the cases to the audience in interactive discussions.

### Learning objectives

At the end of these workshops, participants will be able to:

- interpret drug concentrations in blood and give recommendations for clinical decision making;
- give recommendations in case of adverse drug reactions;
- find out if low drug concentrations are due to poor adherence or due to rapid clearance;
- decide if the dose should be maintained in spite of high drug concentrations.

### Educational need addressed

Hospital pharmacists need to understand how to optimise the dose of antiepileptic and antipsychotic drugs to the individual patients' needs.

**Keywords:** clinical case, pharmacogenetic test, neuropsychiatric drugs.

### “Clinical cases on dose adjustments based on TDM of immunosuppressive and oncolytic agents”

*Dr Erik van Maarseveen [6], University Medical Center Utrecht, The Netherlands*

### Link to EHP Statements

- Section 4, Statement 4.1, 4.3, 4.8
- Section 5, Statement 5.1

### Abstract

The workshop is linked to the oral presentation *TDM and dose optimisation of immunosuppressive and oncolytic agents*. TDM in oncology is rapidly gaining interest. TDM has been implemented for small molecules such as busulfan and paclitaxel as the evidence of added value of TDM to clinical outcomes builds up for these agents. Also, TDM for targeted and bio-based therapies is emerging.

In the workshop, practical examples from the clinical practice will be presented, so that attendants can actually experiment at TDM and see the results and clinical impact of dose adjustment.

### Learning objectives

At the end of these workshops, participants will be able to:

- understand current TDM concepts of oncolytic and immunosuppressive agents;

- implement TDM of oncolytics and immunosuppressants.

### **Educational need addressed**

Hospital pharmacists need to understand how to optimise the dose of immunosuppressive and oncolytic agents.

**Keywords:** clinical case, dose adjustment, immunosuppressive and oncolytic agents,

### **“Interpretation of measured concentration based on comedications and patient's characteristics”**

*Prof Dr Azucena Aldaz Pastor [2], Clínica Universidad de Navarra, Spain*

*Prof Dr Patricio Más, Head of the Pharmacokinetic Unit of the University Hospital of Alicante, Spain*

### **Linked to EAHP Statements**

- Section 4, Statement 4.1, 4.3, 4.8
- Section 5, Statement 5.1

### **Abstract**

The workshop will be linked to *Practical consideration to TDM* and will be organized as the presentation of several clinical cases of dosage adjustment. The workshop will include clinical case of voriconazole and tacrolimus (both the interaction and pharmacogenetics would be considered).

### **Learning objectives**

At the end of these workshops, participants will be able to:

- interpret measured drug concentrations based on patient's characteristics;
- understand the need for dose adjustment.

### **Educational need addressed**

Hospital pharmacists need to understand how patient's characteristics influence interpretation of measured drug concentration.

**Keywords:** comedication, drug-drug interaction, patient's characteristics, voriconazole, tacrolimus

### **“Business case” on implementation of TDM in hospital**

*Antonio Gouveia [8], Insituto Portugues de Oncologia de Lisboa, Portugal*

## Linked to EAHP Statements

- Section 4, Statement 4.1, 4.3, 4.8
- Section 5, Statement 5.1

### Abstract

To implement TDM and dose optimisation, especially in more complex cases, is often seen as daunting task for hospital pharmacists. In this workshop we will show how bussulfan TDM and dose adjustment was implemented in an oncology hospital, with no additional resources. The key for success was collaboration between hospital, university and an external partner. The success of this example should motivate attendants to develop and discuss their own business case, and this could be an important take home message.

### Learning objectives

At the end of these workshops, participants will be able to:

- describe the difficulties and solutions for the implementation of a TDM program in an environment of scarce resources;
- describe, present and discuss a business plan to implement such a program in their own hospital setting.

### Educational need addressed

Hospital pharmacists need to be familiar with solutions for the implementation of a TDM program in hospital settings.

**Keywords:** business case, bussulfan, collaboration, TDM service.

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### Links

[1] <http://www.eahp.eu/content/prof-branislava-miljkovi%C4%87> [2] <http://www.eahp.eu/content/prof-dr-azucena-aldaz-pastor> [3] <http://www.eahp.eu/content/kees-neef> [4] <http://www.eahp.eu/content/prof-dr-daniel-j-touw> [5] <http://www.eahp.eu/content/prof-dr-christoph-hiemke> [6] <http://www.eahp.eu/content/dr-erik-van-maarseveen> [7] <http://www.eahp.eu/content/nieko-punt> [8] <http://www.eahp.eu/content/antonio-gouveia>