

Observational Plan

PhytoVIS Project  
- Productive Phase -

Investigation of Experience with the Use of Herbal Medicinal Products  
(Phytopharmaceuticals) based on an online questionnaire

Prepared According to the Standards of the European Network of Centres for  
Pharmacoepidemiology and Pharmacovigilance

EMA/95098/2010 Rev. 2

18 June 2013

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## List of Abbreviations

ADR	Adverse drug reactions
AMG	Arzneimittelgesetz (Medicinal Products Act)
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
BVL	Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (Federal Office of Consumer Protection and Food Safety)
CGI-E	Clinical Global Impression Scale – Efficacy
DIMDI	Deutsches Institut für Medizinische Dokumentation und Information (German Institute of Medical Documentation and Information)
EMA	European Medicines Agency
IMSIE-MI	Institut für Medizinische Statistik, Informatik und Epidemiologie – Medizinische Informatik (Institute of Medical Statistics, Informatics and Epidemiology – Medical Informatics)
MENSSANA	Mobile Expert and Networking System for Systematic Analysis of Nutrition-Based Allergies
MedDRA	Medical Dictionary for Regulatory Activities
MPG	Medizinproduktegesetz (Medical Devices Act)
PEI	Paul-Ehrlich-Institut – Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel (Federal Institute for Vaccines and Biomedicines)

## Outline

### PhytoVIS Project

Investigation of Experience with the Use of Herbal Medicinal Products  
(Phytopharmaceuticals) based on an online questionnaire

Objective of the survey:	Investigation of experience with the use of herbal medicinal products
Scope of documentation:	Approx. 20,000 data sets
Primary endpoint:	Efficacy and tolerability of the products (user's opinion)
Secondary endpoint:	Acquisition and recommendation of the products
Inclusion criteria:	Individuals who at the time of the survey used herbal medicinal products during the previous eight weeks
Exclusion criteria:	None
Statistical planning:	Descriptive statistics
Interim report:	Yearly
Time span:	End of April 2014 to April 2016 (possible extension)

## Introduction

With few exceptions, most phytopharmaceuticals were excluded from refunding by statutory health insurance funds in Germany upon introduction of the Health Care Reform Act (Gesundheitsmodernisierungsgesetz) in 2004. Such products can be divided into pharmacy-only medicine and general sale list medicine.

While these products had previously been dispensed to a large extent on doctor's orders, afterwards they almost completely changed over to the area of self-medication (1, 2). As a result, the monitoring of treatment by doctors, who until then had still been able to prescribe herbal medicinal products, is disappearing more and more in phytotherapy in Germany. The only possibility remaining for physicians in Germany was to issue private prescriptions. They were intended to serve as a reminder for the patient and to provide pharmacists with important information with respect to the medicine recommended by the physician (3). Documentation and patient compliance are therefore difficult to retrace, if at all.

Up to now, no extensive use has been made of the possibility of obtaining data on the side effects and tolerability of medicinal products at the dispensing site "pharmacy". The information on phytopharmaceuticals currently documented in Germany is largely limited to sales figures and the rather rare reports of adverse drug reactions (ADR). Further data, such as more detailed product information or reasons for use, are not usually documented.

### **PhytoVIS**

Against this background, the PhytoVIS project began in 2011 with the intention of gaining further knowledge in the area of healthcare research of phytopharmaceuticals. Its aim was to develop an online instrument with which physicians and pharmacists could document, in retrospect, the experience gained by their patients/customers with all herbal preparations available in Germany and Switzerland.

The testing/validation of PhytoVIS in the previous, successfully completed phase (pilot phase) consisted on the one hand of the handling of the user interface and, on the other hand, the guarantee of a reliable environment for recording valid data.

## 1. Question / Aim of this Survey

The aim of the productive phase is to gain more experience with the use of the instrument PhytoVIS under real study conditions. In the process, the focus will not be placed on particular target groups, but instead on all natural persons who used a phytopharmaceutical product during the eight weeks prior to the survey.

The purpose of PhytoVIS is not to record data providing proof of efficacy for specific phytopharmaceuticals, as this is not possible within the framework of observational studies. Instead, its aim is to determine which effect the patient actually experiences under the overall therapeutic intervention. This is done bearing in mind that besides therapeutic interventions, certainly many other influencing factors play a role, not least the spontaneous course of the diseases treated.

With regard to undesired effects as well, a causal connection is not possible, e.g., with the application of certain products or with other therapeutic interventions. Also, the legal registration system should not and cannot be duplicated. However, it should be ensured that potentially significant adverse events can be presented and thereby be monitored more closely.

By means of the productive phase of PhytoVIS, initial experience gained in the data analyses of the pilot phase is to be analysed further. Particularly the areas of special groups, such as children, pregnant/nursing women and older people, showed interesting, partly significant results on the Clinical Global Impression Scale – Efficacy (CGI-E). These preliminary results, given by the small sample size of only 17 data sets at times, however, should be either substantiated or discarded (4, 5).

## 2. Data Source / Study Population

Data for the PhytoVIS database are to be collected in Germany in pharmacies and doctor's surgeries. Since the regular staff members in such facilities are very occupied with their daily routine work, they will be assisted in conducting the patient survey and data collection by students of human medicine, pharmacy or similar courses of study from university institutions across Germany. These students are in the process of completing internships, writing research or term papers, or fulfilling academic requirements as part of their studies.

The students will be working with internet-enabled tablet computers and entering the data in the database online. To make the interview easier to conduct, the students will be allowed to use a paper version of the data entry sheet while speaking with the patients. Actual data entry, however, must then be completed in a timely manner and as a rule on the same day. Before beginning such work, the students will receive uniform training by the project coordinator.

The aim of the practical section of each student's scientific project is to document a total of approximately 100 product data sets on the use of herbal medicinal products. Subsequently, the students will compile a report about the project, including a description of their personal experience, in order to fulfil a study requirement.

The study population is not restricted in this survey. Any natural person can be interviewed regardless of indication, product use, age, gender, or ethnic group.

### 3. Study Design

Primary endpoint:

Efficacy and tolerability of the products (user's opinion)

Secondary endpoint:

Acquisition and recommendation of the products

The study data will be made anonymous and patients will be interviewed in retrospect. The study is designed as a multicentre, retrospective survey of users, according to the standards of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (6, 7).

Based on the high number of 20,000 expected data sets, statistically sound, differentiated subgroup analyses are possible and planned.

### 4. Endpoints / Study Parameters

Data collection is planned to commence at the end of April 2014. Based on the experience gained in the pilot phase, a total of 20,000 data sets should be obtained in this phase by April 2016.

The individual survey parameters can be divided into the following areas:

- Complaints/illness
  - Enquiry about indication and symptoms of disease or illness
  - Type of treatment (acute, chronic, preventive)
  - Enquiry about perceived severity
    - The Numeric Pain Intensity Scale of 0–5 will be used during the survey to ask about severity of symptoms (8)
- Information on the use of phytopharmaceuticals
  - Name of the product(s)
  - Dosage form

- Time of use after appearance of symptoms
- Frequency, duration, and dose of application
- Onset of action
- Adverse (primary variable) and desired (secondary variable) effects
  - The validated Clinical Global Impression Scale (CGI Efficacy) will be used to record the primary and secondary variables (9, 10)
- Description of possible side effects
- Recommendation of the product(s)
- Supply source of the product(s)
- Accompanying factors/comorbidities
  - Other diseases/illnesses besides the indication already mentioned
  - Intake of other nonherbal medicinal products
- Basic patient data
  - Age
    - In particular, categorisation of paediatric patients by age is in accordance with the European Medicines Agency guideline (CPMP/ICH/2711/99) (11)
  - Gender
  - Use during a possible pregnancy or while nursing
  - Free text field for possible comments / case details

## 5. Documentation / Coding Systems

### Documentation system

IMSIE-MI will provide a secured server system by the name of secuTrial<sup>®</sup> for the web-based collection of electronic questionnaire data via the Internet. The entire server environment, and therefore also the questionnaire environment, is hosted by the company iAS GmbH in Berlin, Germany, with which IMSIE-MI has already conducted clinical trials since 2010.

secuTrial<sup>®</sup> is a professional, completely browser-based solution for collecting patient data in clinical or noninterventional studies and patient registries.

The design and development of the questionnaires, validation, and administration of the drafted system environment will be carried out by the Institute of Medical Statistics, Informatics and Epidemiology – Medical Informatics (Department Chair: Univ.-Prof. Dr. med. Ralph Mösges) of the University of Cologne, Germany.

All agreements pertaining to data entry, alterations to the database during the ongoing study, data changes (self-explanatory errors), exclusions (medically or logically implausible entries), and changes in the project status will be recorded in the study-specific Data Handling Report.

### Coding systems

The Medical Dictionary for Regulatory Activities (MedDRA) will be used when coding any reported side effects. Coding will be carried out by a qualified staff member of IMSIE-MI.

The phytopharmaceuticals mentioned in the questionnaire will be selected by means of a database which contains all herbal products distributed in Germany. These data originate from the AMIS (Drug Information System) of the DIMDI (German Institute of Medical Documentation and Information). This system contains data from the German drug regulatory authorities BfArM (Federal Institute for Drugs and Medical Devices), PEI (Paul-Ehrlich-Institute – Federal Institute for Vaccines and Biomedicines), and BVL (Federal Agency for Consumer Protection and Food Safety).

## 6. Definition and Measurement of Exposure

In this study, only the retrospective use of medicinal products – here: phytopharmaceuticals – will be documented. Medicinal products will not be recommended or administered.

The only inclusion criterion is that application or use of herbal medicinal product(s) must have taken place within the previous eight weeks.

The questionnaire contains product-related questions as to dosage form, dose, frequency of use, duration of use, onset of action, relation of therapeutic effect / side effects, and the description of possible side effects. This list of questions, however, extends across indications

and products, meaning that observations dependent upon specific doses or durations cannot be defined in advance. In addition, this is a one-time, anonymised, retrospective survey that does not allow for a comparison between times during the course of product use.

## 7. Definition and Measurement of Endpoints

### **Primary endpoint:**

Efficacy and tolerability of the products (user's opinion)

The validated Clinical Global Impression Scale - Efficacy (CGI-E) will be used to record the primary and secondary outcome variables (9, 10). The CGI-E scale depicts a 16-field matrix, asking for the relation of side effects to a therapeutic effect, in which each field is assessed with a score between a minimum of 0.25 and a maximum of 4. If the efficacy index is above a value of 1.00, the therapeutic effect outweighs the side effects (>1–2 = marginal efficacy advantage vs. side effects; 3 = moderate efficacy in the absence of side effects; 4 = marked efficacy in the absence of side effects). At an index of 1.00, the effects counterbalance each other, and at a score of < 1, the side effects outweigh the therapeutic effect (12).

### **Secondary endpoint:**

Acquisition and recommendation of the products

This endpoint serves to aid healthcare research on phytopharmaceuticals in Germany and consists of the following two questions:

#### **1. The product was recommended by / prescribed by:**

*(Multiple answers possible)*

<input type="checkbox"/>	Pharmacist	<input type="checkbox"/>	Books
<input type="checkbox"/>	Physician	<input type="checkbox"/>	Internet
<input type="checkbox"/>	Other health care professional	<input type="checkbox"/>	Advertisement
<input type="checkbox"/>	Family / Relatives	<input type="checkbox"/>	Magazines
<input type="checkbox"/>	Friends / Acquaintances	<input type="checkbox"/>	Other, please specify: _____

## 2. Purchased at / Acquired from:

*(Multiple answers possible)*

<input type="checkbox"/>	Pharmacy	<input type="checkbox"/>	Health food shop
<input type="checkbox"/>	Organic food store	<input type="checkbox"/>	Supermarket
<input type="checkbox"/>	Drugstore	<input type="checkbox"/>	Other, please specify:
<input type="checkbox"/>	Online shop		_____

## 8. Bias and Confounders

Patients are to be interviewed by students of human medicine or pharmacy. The survey itself may only take place in medical facilities or pharmacies to clarify any uncertainties by checking with the health care professional on-site. Both of the different branches of study could represent possible confounders with respect to in-depth knowledge about clinical pictures or pharmaceuticals, respectively. The various documentation sites did not reveal any different tendencies in the pilot phase, let alone significant differences.

Prior to beginning data collection, the students will receive uniform training by the project coordinator to ensure the quality of data starting from the very first incoming data set. A manual has defined the procedure to follow when surveying the patients (e.g., no selecting, but rather addressing the next available patient) and the preferred words to use during the interview. This information can also be found in the Data Handling Report. The selection bias in choosing patients and the information bias during the interview should thereby be neutralised.

Biases could arise in the pooled data analyses across indications and products. The corresponding therapeutic effect cannot be measured particularly in cases where the use of products is supposed to counteract the worsening of the patient's disease. For this reason, these data sets must be identified for the respective pooled analyses and evaluated separately. Preventive applications that were included in the pilot phase of the project will therefore be selected in the productive phase beforehand by means of a separate query.

## 9. Analysis Plan

### **Statistical Methods**

All questionnaires with their respective available data will be analysed using the SPSS statistical software package by IBM (Version 22). Besides general outcome measures, subgroup analyses (e.g., age groups, product groups, indication groups, etc.) will also be carried out during the analysis process.

Since the survey is not controlled and will take place only once, the data collected will only undergo descriptive analysis. Categorical data will be presented by means of absolute and percentage frequencies.

After the survey is completed, the analysis strategy will be adapted to the given situation. In the process, it will be determined whether additional analyses appear sensible and should be carried out in the subgroups as well. If applicable, a statistical comparison between the subgroups can also be determined.

## 10. Quality Control / Management / Reporting

### Questionnaire environment

Data will be recorded using the clinical web-based software named secuTrial<sup>®</sup>. This software has been used since 2000 in more than 300 national (i.e., German) and international trials and long-term projects at university institutions, CROs, and pharmaceutical companies.

secuTrial<sup>®</sup> was designed for carrying out trials relating to drug approval and must also fulfil regulatory requirements in the areas of quality management, software development, and FDA/GCP compliance.

The compliance of secuTrial<sup>®</sup> with 21CFR Part11 regularly undergoes independent benchmarking audits, partly in diverse supplier audits. Recently, secuTrial<sup>®</sup> 4.1.0.8 was successfully validated by proDERM GmbH. The audit concludes that the described and practised processes at iAS GmbH ensure that secuTrial<sup>®</sup> – including its future updates – functions according to specifications and that the requirements stated in the specification

sheet are correctly implemented in terms of function. An expert evaluation of compliance prepared by BioMedion arrives at the conclusion that “secuTrial® fulfils all relevant items of the legal requirements set forth in the AMG and 21CRF Part11” (AMG: German Medicinal Products Act). A compliance assessment made by ABB Eutech evaluates secuTrial® as “best practice and best in class practice”.

The questionnaires themselves consist of several required fields in order to avoid missing values. Every questionnaire found in the database can therefore be used for subsequent analyses. Before the statistical analyses begin, each questionnaire will also undergo data review prior to inclusion in order to eliminate medically or logically implausible entries and to ensure validity of the data. At least two reviewers must approve such eliminations. These excluded cases will be recorded along with the reason in the Data Handling Report.

#### IMSIE-MI

IMSIE-MI has been successfully certified by TÜV Rheinland for the audit norm ISO 9001:2008 for the following areas of application:

Planning, implementation, informatics, statistical analysis and publication of clinical studies within the scope of the AMG, outside of the scope of the MPG, and noninterventional studies.

This observational plan was prepared according to the guidelines issued by the Ethics Committee in Cologne. In addition, it meets the quality standards implemented within the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (EMA/95098/2010 Rev.2, 18 June 2013).

Furthermore, IMSIE-MI is in possession of empirical values from the successfully completed project called MENSANA (Mobile Expert and Networking System for Systematic Analysis of Nutrition-Based Allergies), which was conducted under the direction of the institute “Centre de Recherche Public Henri Tudor” in Luxemburg (*Application number 09-088*). Among other things, an online questionnaire was developed in this project to collect over 200 pseudonymous patient data within the scope of an observational study.

The productive phase of PhytoVIS has been preceded by a pilot phase (*Application number 12-057*) which, having over 2,000 incoming data sets, was successfully completed and approved by the Ethics Committee Cologne. IMSIE-MI also intends to publish the results of the productive phase in the context of scientific articles.

#### Documentation sites / Data entry staff

The respective data entry staff will receive training in handling the system before the survey begins. Besides the live system, a test environment will also be available in which the designated staff can test data entry in advance.

These staff members will receive the following documents in advance:

- Participation Information
- User Manual
- Declaration of Consent

Access to the online questionnaire is only possible with a user name and password, which at the same time are to serve as identification for the analysis. For this purpose, the interviewer's first and last name as well as a current and valid e-mail address are required in order to receive his/her login details (link, user name, and password). These personal data, however, are only needed for the purpose of communication and technical administration of the questionnaire environment.

Only after the project students/interviewers sign the Declaration of Consent form on data protection and the Participation Information form about the online survey and submit them to IMSIE-MI do they receive an e-mail from IMSIE-MI, which includes an individualised user name and password for entering actual patient data into the live system. After completion of the survey, all data will be stored and archived according to currently valid directives (at least 10 years).

## Patient Data

The collected patient data cannot be traced back to the interviewee. Only an anonymous interview is available for the analysis.

The data protection officer of the University of Cologne, Mr. Alexander May, provided comprehensive initial counselling on data protection laws with respect to the design of the questionnaire, data protection as a whole, and the Declaration of Consent form from the data entry centres on 6 March 2012 at 10:00 a.m.

### Conclusion:

*Personal data that could have enabled identification of patients based on their being outliers (example age 109) were neutralised by building clusters. Due to lacking significance, the items height and weight were removed from the questionnaires by means of cluster building. Anonymity of the patient data was thereby also ensured. The patient data therefore cannot be traced back to the respective interviewee.*

*The possibility of data protection infringement, which could have occurred through identification of the person entering the data, was eliminated by requiring all participating data entry centres to sign the Declaration of Consent form. Furthermore, the principles of data processing were described in a comprehensive Participation Information form. Likewise, the principles of statistical analyses that are to be carried out based on the entered data were explained. Access to the online questionnaire is only possible using an individual code (individual with respect to the data entry centre), which at the same time serves as identification in the analysis.*

*In the context of the intended scientific publications, no evaluations of individual cases will be published that could endanger the anonymity of the data entry centre or an individual patient.*

*E-mail addresses from the networks of the respective project members will only be passed on to IMSIE-MI after a Declaration of Consent form has been signed. After*

*the login details have been sent, the e-mail address is required in order to disclose a forgotten password to the participant or to confirm a new password.*

### Publication

This project will be registered in the “ENCePP Electronic Register of Studies” of the EMA study database<sup>1</sup> in accordance with the requirements for pharmacoepidemiological and pharmacovigilance studies, and the results will be published in a scientific journal in any event.

Data in anonymous form will be made available to Kooperation Phytopharmaka GbR and IMSIE-MI, University of Cologne, for scientific purposes.

## 11. Ethics / Legal Requirements

Since this is a one-time online survey on users’ past experience, it is not subject to the legal obligations to notify authorities according to the AMG (Medicinal Products Act) and MPG (Medical Devices Act) in Germany. This project will be submitted to the Ethics Committee Cologne for assessment of data protection and ethics, and accordingly for evaluation.

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<sup>1</sup> See: <http://www.encepp.eu/encepp/addstudy.jsp>

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