Observation plan

PhytoVIS project

- Productive phase II -

Retrospective online survey
to investigate experiences with the use
with herbal medicines (phytopharmaceuticals)

Prepared in accordance with the standards of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

EMA/95098/2010 Rev.11

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1 List of abbreviations

BfArM	Federal Institute for Drugs and Medical Devices
CCC	ClinCompetence Cologne GmbH
CGI-E	Clinical Global Impression Scale – Efficacy
CRO	Contract Research Organisation, contract research institute
DIMDI	German Institute for Medical Documentation and Information
EMA	European Medicines Agency
EnCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
PEI	Paul Ehrlich Institute – Federal Institute for Vaccines and Biomedical Medicinal Products
MedDRA	Medical Dictionary for Regulatory Activities

2 Synopsis

PhytoVIS project Productive phase II

Retrospective online survey

to investigate user experiences

with herbal medicinal products (phytopharmaceuticals)

Applicant	Prof. Dr. med. Dipl.-Ing. Ralph Mösges Institute for Medical Statistics and Bioinformatics at the University of Cologne Robert-Koch-Str. 10 50931 Cologne
Study	Prof. Dr. med. Dipl.-Ing. Ralph Mösges Institute for Medical Statistics and Bioinformatics at the University of Cologne Robert-Koch-Str. 10 50931 Cologne Tel Email: ralph.moesges@uni-koeln.de
Funding	Cooperation with Phytopharmaka Office Plittersdorfer Str. 218 53173 Bonn
CRO	ClinCompetence Cologne GmbH Theodor-Heuss-Ring 14 50668 Cologne
Title of the study	Retrospective online survey to investigate user experiences with herbal medicines (phytopharmaceuticals)
Objective	To collect user experiences with herbal medicines
Study	Anonymous, one-time retrospective survey
Patient population	Inclusion criteria Persons who had used herbal medicinal products in the last eight weeks at the time of the survey Exclusion None
Sample size	Approximately 20,000 data sets
Primary endpoint:	Effectiveness and tolerability of the products (assessed by the user) using CGI-E (Clinical Global Impression Scale – Efficacy)

Secondary endpoints:	• Source of purchase and recommendation of the products • Reported indication and symptoms of the disease • Duration of use, last intake and effect of the product • Duration and severity of symptoms • Dosage form, dosage, duration and frequency of use • Onset of action • Side effects that required a visit to the doctor • Source of recommendation and source of purchase • Other diseases and medicines • Age group at start of use • Gender
Statistical planning:	Descriptive statistics
Study duration:	End of June 2025 to April 2027 (possible extension)

3 Signatures

Study director

Prof. Dr. med. Ralph Mösges Place and date:

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Signature:

Author of the observation plan

PD Dr. Esther Raskopf Place and date:

Signature:

Signature:

Cooperation Phytopharmaceuticals

Dr. Barbara Steinhoff Place and date:

……

Signature:

4 Introduction

With a few exceptions, phytopharmaceuticals have now become part of self-medication (1). This makes it difficult or even impossible to track their use by patients and document it.

So far, there's been little use of the chance to get info on how phytopharmaceuticals are used and tolerated at the point of recommendation (e.g. doctor's office or pharmacy). The info collected in Germany on phytopharmaceuticals is currently mostly limited to sales figures and the rather rare reports of adverse drug reactions.

4.1 PhytoVIS

Against this background, the PhytoVIS project was launched in 2011 with the aim of advancing knowledge in the field of phyto-pharmaceuticals in healthcare. The goal was to develop an online tool that would enable doctors and pharmacists to retrospectively record their patients'/customers' experiences with all herbal preparations available in Germany.

After a successful evaluation and pilot phase, the production phase followed, in which 20,000 patients/customers were surveyed on their use of herbal medicines between 2014 and 2017, resulting in 24,000 data sets being evaluated.

4.2 Research question/objectives

The new productive phase of PhytoVIS is intended to supplement the results obtained in the data analyses of the previous productive phase.

The productive phase II is intended to gain further experience with the application of the PhytoVIS tool under real-life study conditions. It covers all natural persons who have used a phytopharmaceutical in the last eight weeks at the time of the survey. The purpose of PhytoVIS is not to collect data on the specific efficacy of phytopharmaceuticals – this is not possible within the framework of observational studies. Rather, the aim is to record how patients assess the effect within the overall therapeutic intervention. This is done in the knowledge that, in addition to the therapeutic interventions, many other influencing factors, such as the spontaneous course of the diseases being treated, play a role.

The focus should be shifted towards collecting data from children and adolescents, preferably through surveys conducted by paediatricians.

These special groups in particular show some significant results in the Clinical Global Impression Scale – Efficacy (CGI-E), which, however, need to be investigated further by increasing the number of cases (1 ,2).

With regard to adverse drug reactions, it is not possible to establish a causal link, e.g. with the use of certain products or with other therapeutic interventions. Furthermore, the statutory reporting system should not and cannot be duplicated. However, it will be ensured that adverse drug reactions that have led to a visit to a doctor can be reported via the questionnaire.

Due to the high number of data sets expected – a further 20,000 are targeted – statistically sound, differentiated subgroup analyses are also possible and planned.

5 Study population

The study population is not limited in this survey. Every natural person is to be surveyed, regardless of indication, product use, age, gender or ethnic origin. However, data on paediatric patients should be collected preferentially, e.g. by choosing an appropriate location for the survey, such as a paediatric doctor's office.

5.1 Inclusion

The only inclusion criterion is that herbal medicinal products must have been used within the last eight weeks.

There are no exclusion criteria for this study.

6 Study

The study will be conducted anonymously and retrospectively as a one-time survey. The design is multicentre – data will be collected mainly in doctors' offices and all points of sale for medicinal products (especially pharmacies).

Data collection is scheduled to begin in June 2025. Based on experience from the previous productive phase, the aim is to collect a total of 20,000 data sets by April 2027. As the regular staff at the herbal medicine dispensing points are very busy with their day-to-day work, they will be supported in the patient survey and data collection by students of human medicine, pharmacy or similar courses from universities throughout Germany. These students will thus

complete internships, term papers, seminar papers or similar coursework as part of their studies.

The students work with their smartphones or other mobile devices and enter the data online into the database. Before starting this activity, the students receive standardised training from the project coordinator. This training can also be done online as self-training.

The aim of the students' scientific project work is to survey approximately 100 patients who have used herbal medicines and to collect at least 100 product data records.

7 Documentation/coding systems

7.1 Documentation system

ClinCompetence Cologne GmbH (CCC) will provide a secure server system for web-based recording of the free online survey application "Lime Survey" via the Internet. When creating the questionnaire, special attention will be paid to ensuring that the survey can be conducted using a smartphone or mobile device.

LimeSurvey is a professional, browser-based, clear solution for collecting anonymous patient data in retrospective, non-interventional studies and patient registries. The system is written in the PHP programming language and has a MySQL, PostgreSQL or MSSQL database. The open source software LimeSurvey is easy to use and requires no programming knowledge, which makes data entry and storage a breeze.

CCC is responsible for questionnaire development, validation and administration of the system environment.

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

7.2 Coding systems

The Medical Dictionary for Regulatory Activities (MedDRA) in the version current at the time of coding is used to code the reported adverse events. Coding is carried out by a qualified employee.

The selection of herbal medicinal products is carried out within the questionnaire using a database that lists all herbal medicinal products marketed in Germany. This data comes from

the drug information system of the DIMDI (German Institute for Medical Documentation and Information), which is composed of data from the drug approval authorities BfArM (Federal Institute for Drugs and Medical Devices), PEI (Paul Ehrlich Institute – Federal Institute for Vaccines and Biomedical Medicinal Products) and BVL (Federal Office for Consumer Protection and Food Safety).

8 Definition and measurement of expo sition

In this study, the use of medicinal products – in this case phytopharmaceuticals – is recorded exclusively retrospectively. No recommendations or administration of medicinal products are made. In addition, the number of days/weeks since use is recorded.

The questionnaire contains product-related questions on the dosage form, dosage, frequency of use, duration of use, onset of action, relationship between therapeutic effect and side effects, and a description of possible side effects. However, this questionnaire covers all indications and products, so that specific dosages or observations dependent on the duration of use cannot be defined in advance. In addition, this is a one-time, anonymous retrospective survey that does not allow for comparisons between different points in time.

9 Definition and measurement of endpoints

9.1 Primary endpoint

Efficacy and tolerability of the products (user assessment)

The validated Clinical Global Impression Scale – Efficacy (CGI-E) is used to record the primary and secondary endpoints ((6 ,7). The CGI-E scale is a 16-field matrix that shows the relationship between tolerability and therapeutic effect. Each field is assigned a score between 0.25 and 4.00. If the efficacy index is above 1.00, the therapeutic effect outweighs the adverse drug reactions in the respective dimension strength (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). With an index of 1.00, the effects cancel each other out. With a score of <1.00, the adverse drug effects outweigh the therapeutic effect (9).

9.2 Secondary endpoints

- Location of survey
  - Federal state
  - Place of administration
- Complaints/illness
  - Questionnaire on indication and symptoms
  - Type of treatment (acute, chronic, preventive)
  - Question about perceived severity (based on the Numeric Pain Intensity Scale (5))
- Information on the use of phytopharmaceuticals
  - Name of the product(s)
  - Dosage
  - Time of application after onset of symptoms
  - Frequency, duration and dose of use
  - Time of onset of effect
  - Description of possible side effects for which a doctor was consulted
  - Source of recommendation for the product
  - Source of the product
- Accompanying factors/comorbidities
  - Other diseases in addition to the indication already mentioned
  - Use of other medicines
- Basic patient data
  - Age
    - The age classification of paediatric patients in particular is based on the guidelines of the European Medicines Agency (CPMP/ICH/2711/99) (8)
  - Gender
  - Use during pregnancy or while breastfeeding
- General survey data
  - Comment on the case by the interviewer

10 Bias and confounders

The survey is preferably conducted by students of human medicine and pharmacy. The different disciplines could represent a potential confounding factor in terms of specialist

knowledge of the clinical picture or pharmacology. The different documentation centres did not show any different trends, let alone significant differences, in the pilot phase.

Before data collection begins, students receive standard training from the project coordinator to ensure data quality from the very first data set received. A manual sets out the procedure to be followed when questioning patients (e.g. no selection, but preferably addressing the next paediatric patient) and the wording to be used in the questionnaire. This is intended to neutralise selection bias in patient selection and information bias during the questionnaire.

Distortions could arise in the pooled data analyses across indications and products. The therapeutic effect is particularly difficult to measure for product applications intended to counteract the deterioration of a condition. These data sets must therefore be identified and evaluated separately for the corresponding pooled analyses. The preventive applications that were included in the pilot phase of the project will therefore be selected in advance by means of a separate query during the production phase.

11 Statistical analysis plan

All questionnaires with the available data will be evaluated using IBM's SPSS statistical software or comparable programmes in the version available at the time of evaluation. In addition to the general target parameters, subgroup analyses (e.g. age groups, product groups, indication groups, etc.) will also be carried out as part of the evaluation.

Since the survey is not controlled and only takes place once, the data obtained is evaluated purely descriptively. Categorical data is presented using absolute and percentage frequencies. Numerical data is presented using the mean, median, standard deviation, 25/75 percentile, and minimum and maximum values.

After completion of the survey, the evaluation strategy is adapted to the given situation in an evaluation meeting. It is determined whether additional analyses appear useful and should be carried out in sub-collectives. If necessary, a statistical comparison between the subgroups can also be determined.

12 Quality assurance/management/reporting

This observation plan was drawn up in accordance with the guidelines of the Working Group of Medical Ethics Committees. It also complies with the quality standards set out in the

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (EMA/95098/2010 Rev.11).

This productive phase of PhytoVIS was preceded by a previous productive phase *(application number: 14-101)*, which was successfully completed with almost 25,000 data records received. Publication in scientific publications is also planned during the productive phase.

12.1 The questionnaire environment

Data collection is carried out using the open source software Lime Survey.

Since 2000, the software has been used in more than 300 national and international studies and long-term projects at university institutions, CROs (contract research organisations) and pharmaceutical companies.

The questionnaire consists of mandatory fields to avoid missing values. This ensures that every questionnaire in the database can be used for subsequent analyses. Before the final statistical analyses are carried out, each questionnaire also undergoes a data review to identify medically or logically implausible entries and ensure data validity. These cases are recorded in the Data Handling Report.

12.2 Institute for Medical Statistics and Bioinformatics

The *Medical Statistics* Working Group at the Institute for Medical Statistics and Bioinformatics (IMSB) performs the statistical analysis of the data.

The IMSB's *Medical Statistics working group* focuses on the application of statistical methods in medicine, advising and supporting medical research projects, developing new statistical methods for these projects, and representing the field in teaching. The working group has carried out numerous subgroup analyses of the previous productive phase.

The predecessor institution of the IMSB (Institute for Medical Statistics, Informatics and Epidemiology, IMSIE) developed the database for the productive phase, supervised the project and analysed the data.

12.3 ClinCompetence Cologne GmbH

ClinCompetence Cologne GmbH (CCC) is a CRO whose main areas of expertise and research focus are in allergology, infectiology and ear, nose and throat medicine. Its scientific mission

is to further develop and conduct basic research and patient-oriented clinical research, always striving to improve patient care while ensuring continuous improvement of the quality management system.

In compliance with ethical standards and international and local legal requirements, the standard operating procedures and quality assurance are verified and certified according to ISO 9001.

12.4 The documentation centres / data providers

The respective data entry clerks will receive training in how to use the system before the survey begins. In addition, a test environment will be available alongside the production environment, which data entry clerks can use to test data entry in advance.

They will receive the following documents in advance:

- Participation information for students
- User manual
- Declaration of consent for students

Only after the declaration of consent to data protection and participation in the online survey has been signed by the students will they receive an individualised user name and password by email to enter the real patient data.

12.5 Data security and data protection

The patient data collected does not allow any conclusions to be drawn about the person who was surveyed. The survey is completely anonymous. The data protection officer is Dr Susann Fragel (CCC).

12.6 Public

This project is registered in accordance with the guidelines for pharmacoepidemiological and pharmacovigilance studies in the "ENCePP Electronic Register of studies" of the EMA

(European Medicines Agency) study database[1] . The results will be published in scientific journals.

The anonymised data will be made available to Phytopharmaka GbR and the CCC for scientific purposes and are the property of Phytopharmaka GbR.

13 Ethics / Legal requirements

As this is a one-off online survey on past experiences of use, there are no legal reporting requirements under the German Medicines Act. This project will be submitted to the Ethics Committee of the University Hospital of Cologne for data protection and ethical evaluation and comment.

13.1 Consent to data processing

Before the survey begins, the respondent's consent to data processing is obtained. This is done by means of the query " Do you consent to the anonymous collection of your data? ". The answer is documented on the questionnaire. The respondent may withdraw their consent at any time during the survey and also request the deletion of the data collected up to that point.

14 Literature

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[1] See: https://catalogues.ema.europa.eu/catalogue-rwd-studies

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