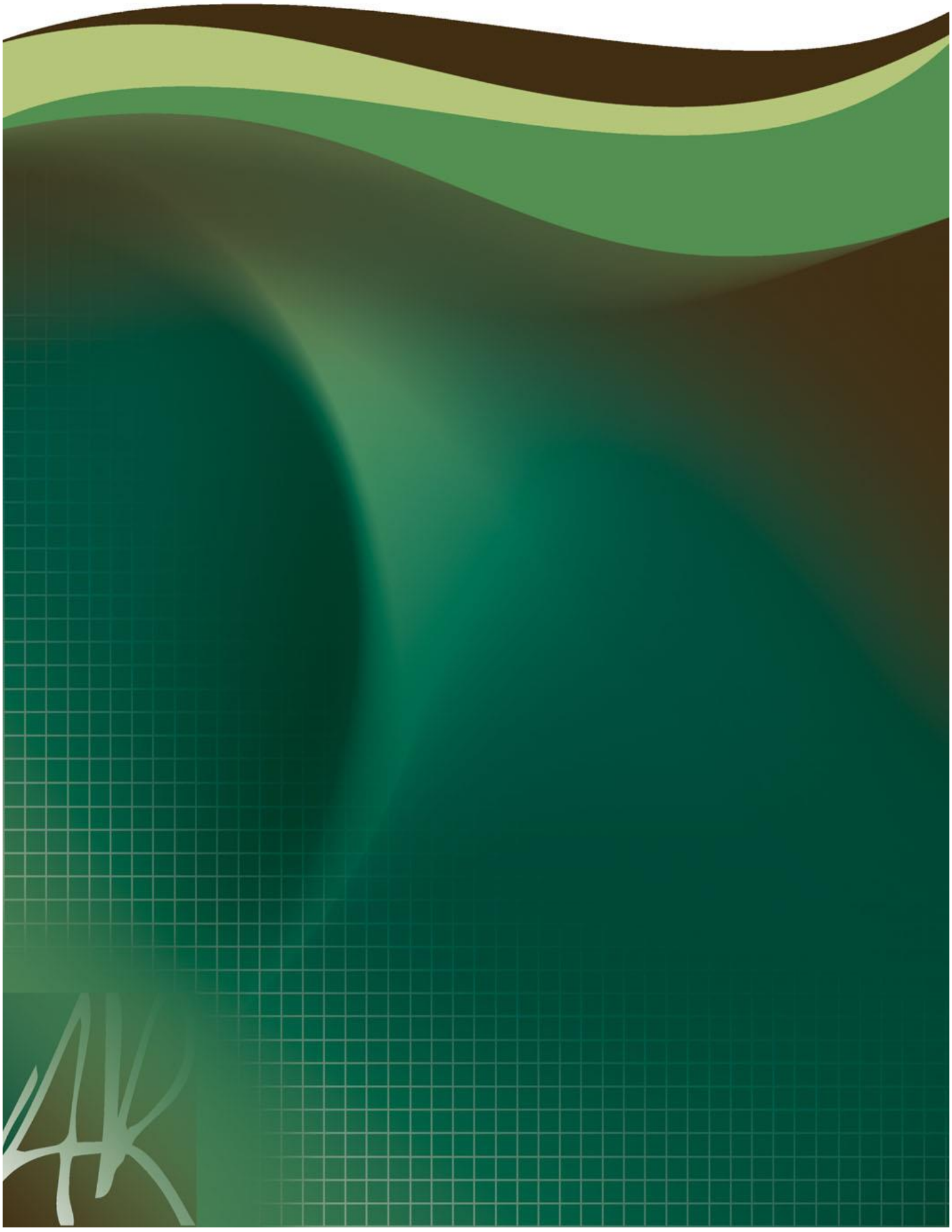
AdWare
RESEARCH

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# GENERAL INTRODUCTION

AdWare Research was established in 1997 and it is a dynamically developing pre-clinical and clinical data-management and biostatistics provider company. Its main activities are data-management, biostatistics, quality assurance, independent audit, education and consultancy.

From the starts AdWare operates according to the highest standards and provides its services in accordance with the international regulations. The activities of the company were broadened in 2002 by developing high quality data management software in order to provide comprehensive opportunities to our partners.

With its own developed software (called Mythos) – that is in compliance with 21 CFR Part 11 FDA, and fulfils the criteria of Hungarian and international standards – AdWare ensures the outstanding informatical background of its works. Mythos is a determinant system on the data management market.

AdWare applies CDISC standards.

## Objective

The objective of the company is to provide competitive, high-quality solutions in the field of clinical data-management and biostatistics.

## Vision

AdWare was created as a family business and within 10 years it became one of the market leaders in the Hungarian data-management market. Our vision is to become a significant actor on the international market as well by making use of the national experience.

## Key Client Benefits

The secret of our success lies in our **flexibility**, in the **high quality** with which we satisfy our clients' need, in the **prompt and precise work**, in the fact that we can provide **full-scale services**, and last but not least in the **competitive price** at which we serve our customers.

- **high quality** – it is ensured by keeping the national and international regulations
- **more than one decade national and international experience** – since 1997 AdWare has taken part in several national and international data-management and biostatistics projects
- **professional team –** improving our colleagues' knowledge and labour skills is our benefit as well that is why we put high emphasis on training our staff.
- **competitive price –** see an indicative quotation below

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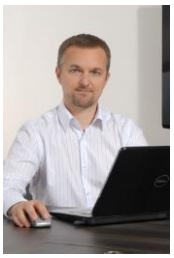
## MANAGEMENT

| | |
|---|---|
| **Zsuzsanna Papp phd. – Managing Director**<br>  | • Pharmacist phd<br>• 5 years work experience at National Institute of Psychiatry and Neurology Dept. of Pathochemistry Lab. Scientist<br>• Managing Director since 1997<br>• 15 years experience in data-management and biostatistics<br>• 21 years experience in quality assurance (GCP, GLP, ISO systems)<br>• 20 years experience in toxicology |
| **Bence Balint – Managing Director**<br>  | • Chemical Engineer<br>• Managing Director since 1999<br>• 10 years experience in data-management and biostatistics<br>• 10 years experience in quality assurance (GCP, GLP, ISO systems) |
| **Laszlo Rak – Scientific Director**<br>  | • BME - Technical University of Budapest M.Sc. - Faculty of Electrical Engineering and Information Science, Department of Telecommunication and Telematics, Second Department of Mobile Communication<br>• 5 years in data management<br>• Data Management System Specification and Validation<br>• Biostatistics knowledge<br>• Take part in more than 30 studies<br>• Continuous learning |
| **Mariann Borsos – Biostatistician**<br>  | • Applied Mathematician specialized in statistics and optimization<br>• 6 years experience in biostatistics (designing and analysing pre-clinical, Phase I, Phase II, Phase IV and PMS studies)<br>• participation in several international projects<br>• Member of the Hungarian Society of Clinical Biostatistics and the International Society of Clinical Biostatistics |

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| | |
|---|---|
| **Aniko Cserny – Project Manager**<br>  | • Economist (BA from University of Lincoln, MSc from University of Pecs)<br>• Clinical Trial Assistant certificate<br>• 7 years experience in business development and international marketing |

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## PROJECT MANAGEMENT

Full scale management of clinical trial from application, selecting sites (phase I-IV, GLP analytical site), till involving appropriate experts for conducting and monitoring trials in the area of pharmaceutical, dietary supplement, functional food, human medical devices and cosmetics research.

## DATA-MANAGEMENT AND BIOSTATISTICS SERVICES

*AdWare Research provide*s data management and biostatistics services according to its SOPs, regulatory requirements, and international guidelines (FDA 21CFR Part11 and ICH E3, E6, E9, etc.).
The informatical basis of our service is the Mythos CDMS that makes regulation-compatible data collecting and cleaning possible. SAS programme is used for data processing and for doing statistical analysis.

**The main activity of data management and biostatistics:**

1. Sample size determination
2. Writing the data management & statistical part of the study protocol,
3. Randomization procedures & generation of randomization envelops
4. Designing and preparing the CRFs
5. Preparing and validating the data entry system corresponding to the study protocol (Using ORACLE® database)
6. Writing the Statistical Analysis Plan (SAP)
7. Writing the Data Cleaning Plan (DCP)
8. Single or double data entry
9. MedDRA coding under medical control
10. Handling the Data Clarification Forms (DCF) or Data Query Forms (DQF)
11. Database closing
12. Statistical analyses according to SAP using SAS® software
13. Preparing the tabulated forms
14. Writing the statistical report according to ICH E3 (Structure and Content of Clinical Study Reports)
15. Data-mining
16. QA of the above activity according to ICH E6 (Guideline for Good Clinical Practice)

### 1. SAMPLE SIZE DETERMINATION

We can be at our clients' disposal with the following services:

- ® choosing the appropriate test statistic,
- ® determining the null hypothesis,
- ® determining the alternative (working) hypothesis
- ® determining the minimally relevant change that should be detected (if appropriate)
- ® determining the probability of wrong rejecting the null hypothesis (the Type I error),
- ® determining the probability of wrong failing to reject the null hypothesis (the Type II error),

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® determining the approach dealing with treatment withdrawals and protocol violations,

The method by which the sample size is calculated is described in the protocol, together with the applied estimates of the parameters used in the calculations (such as variances, mean values, response rates, event rates gained from earlier studies or from the literature, etc.)

Sample size determination is done by SAS® software or nQuery Advisor®.

## 2. WRITING THE DATA MANAGEMENT & BIOSTATISTICS PART OF THE STUDY PROTOCOL

The biostatistics part of the study protocol includes the followings:

© A detailed description of the study variables and the statistical methods to be applied, including timing of any planned interim analysis
© The number of subjects planned to be enrolled
© Reason for choice of sample size, including reflections on (or calculations of) the power of the study and preclinical or clinical justification
© The level of significance to be used
© Criteria for early termination of the clinical study
© Procedures for handling missing, unused, and extreme data
© Procedures for reporting any deviation(s) from the original statistical plan
© The statistical and data management software(s) to be used

## 3. RANDOMIZATION PROCEDURES & PREPARATION OF RANDOMIZATION ENVELOPS

© The preparation procedure is performed according to our SOPs and the actual study protocol
© Randomization code is generated by using SAS® software or nQuery Advisor®
© The storage and access of the randomization data set is strictly regulated
© One paper copy is sent to the sponsor in a closed envelop, the opening of which is strictly regulated
© Preparation of Closed Randomization Envelopes for the sponsor or study sites

## 4. DESIGN AND PREPARE THE CRFs

© The CRF contains all the information comprised in the protocol
© QA verifies that the information in the protocol and the CRF are the same
© Preparation of CRF Completion Guidelines
© Organization of the printing and distribution of CRFs and the Completion Guidelines

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## 5. PREPARING AND VALIDATING THE DATA ENTRY SYSTEM CORRESPONDING TO THE STUDY PROTOCOL (USING ORACLE® DATABASE)

© We use ORACLE® database, SAS® datasets or SPSS® files to store data
© Single or independent double data entry depending on the Sponsor's requirements
© Interval checks for continuous variables, and dictionary for category or string data variables
© Automatic data entry check according to predefined rules
© CRF review before Screen Testing,
© Preparing Study specific completion guide
© Initial training to data entry staffs
© Security – A) Closed data management system or
B) Open- eCRF data management system (via secure internet connection, individual passwords)
© Source data upload (x-ray, MR, etc.)
© Tailor made eCRF design

## 6. WRITING THE STATISTICAL ANALYSIS PLAN (SAP)

The statistical analysis plan contains a detailed description of the study populations, study variables and the applied statistical methods.

Standard chapters

© Demography and anamnesis - descriptive statistics
© Mock table list
© Safety analysis (performed on safety population) - descriptive statistics and individual lists
- AEs grouped by severity, outcome, relationship to study medication
- AEs summarised by SOC and PT (if required)

Non-standard chapters

© Efficacy analysis
- Primary efficacy analysis performed usually on both ITT and PP population
- Secondary efficacy analysis performed on ITT population only

## 7. WRITING THE DATA CLEANING PLAN (DCP)

Data Cleaning Plan deals with the process of detecting, diagnosing, and editing faulty data:

© Detecting:
- Lack/Excess of data
- Outliers/Inconsistencies
- Strange patterns
- Suspect analysis results

© Diagnosis:
- Errors, missing data
- True extreme
- True normal
- No diagnosis still suspect

© Editing:
- Correction
- Deletion
- Leave unchanged

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## 8. SINGLE OR DOUBLE INDEPENDENT DATA ENTRY

© *SINGLE DATA ENTRY* = data typed into the database by a single individual
© *DOUBLE, INDEPENDENT DATA ENTRY* = data typed by two independent individuals. Data are compared and corrected by the data-manager using Mythos.
© Each action (entry, modification, deletion) is documented in the ***audit trail***.

## 9. MEDDRA CODING UNDER MEDICAL CONTROL

The Scope of MedDRA we use for coding under medical control:

© Diseases
© Diagnoses
© Signs
© Symptoms
© Therapeutic indications
© Investigation names & qualitative results
© Medical & surgical procedures
© Medical, social, family history
© Terms from: COSTART®, WHO-ART®, HARTS®, J-ART®

## 10. HANDLING THE DATA CLARIFICATION FORMS (DCF) OR DATA QUERY FORMS (DQF)

© Each query is checked by data managers and is sent to the investigator
© Modifications are made according to the answers

## 11. DATABASE CLOSING

© Hard database closing is performed by writing it on an archival-grade, write-protected data storage,
© The closed database is stored according to strict regulation in a closed fireproof area

## 12. STATISTICAL ANALYSES ACCORDING TO SAP USING SAS® OR SPSS® SOFTWARE

© The statistical analysis is done by a biostatistician expert according to SAP and our SOPs
© SAS® or SPSS® software is used for data transformation and statistical analysis

## 13. PREPARING AND LISTING THE TABULATED FORMS

© We make tabulated forms using SAS® or SPSS® according to the pre-defined mock tables described in the Statistical Analysis Plan

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## 14. WRITING THE STATISTICAL REPORT ACCORDING TO ICH E3 (STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS)

The statistical report describes the methods and findings of the statistical analysis. The statistical report contains (according to ICH E3 guideline) the following items:

© Objective(s) of the study,
© Study design,
© Data quality controls,
© Treatment Group Comparability (if applicable)
© Efficacy Analysis (Sample Size Estimation, Endpoints, Patient Subsets, Evaluation criteria, Handling of incomplete data, Subset analyses of efficacy)
© Safety Analysis (Patient Included, Endpoints)
© Other Analysis
© Deviations from the SAP
© Statistical Methodology (Statistical Software, Treatment Group Comparability, Efficacy Analyses, Safety Analyses)
© Results (Treatment Group Comparability, Efficacy Analyses, Safety Analyses)
© Conclusions
© Appendices (Summary, Individual data)

## 15. DATA MINING

© The statistical analysis is done by a biostatistician expert.
© SAS® or SPSS® software is used for data transformation and data mining.
© Building and evaluation of models such as prediction, classification, clustering and regression models.
© Presenting the results in tables, graphs and a summary report.

## 15. QA OF THE ABOVE ACTIVITY ACCORDING TO ICH E6 (GUIDELINE FOR GOOD CLINICAL PRACTICE)

Minimum 20 % of the CRFs have to be verified, but of course if it is required 100 % verification is also possible.

# *MYTHOS – THE DATA-MANAGER SOFTWARE OF ADWARE*

Mythos Clinical Data Management System uses Oracle® database to provide secure and traceable data management. The Audit trail function which cannot be switched off records *Who, What, When, Why modified the Original data and what is the New data.*

*Mythos is able to handle both eCRF and paper-based CRF.*

**eCRF**

- **There is no need to install additional software on the user site** - an Internet connection and an Internet Explorer are needed to collect eCRF data.

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- **Secure data transfer and storage** - eCRF data are stored solely in the Mythos Oracle® database, while on the users' side there is not even temporary storage. Data are transferred to the database by saving the actual eCRF page. The system uses secure SSL connection (applying data encryption) for data transfer.

- **Immediate and automatic data monitoring -** the system is programmed for automatic data check which is able to detect data not meeting the previously set requirements (*extreme or logically impossible values, derivative data like BMI, fields compulsory to fill in, chronological order, violation of the time-window, violation of protocol, etc.*).

**Paper-based CRF**

In case of traditional paper-based data recording, it is possible to establish closed network data management systems which do not have access to any external network / Internet.

**Features of the system**

- **Customizable Database -** During database planning process, the Data Manager can easily create the database structure (with the data checks, eCRF format and the eCRF completion guide) which stores the data.

- **User-friendly appearance (like paper based CRFs) with automatic data monitoring function -** The data entry screen visualizes the CRF in a user friendly way, and with showing additional information the clarity of recorded data can be increased. As we have clear data, database closing and evaluation processes are more efficient.

- **Semi-automatic generation of Queries -** Each field which can be determined at the time of the creation of the query is filled in automatically and cannot be changed. Query is identified by a unique number - *query ID* - which cannot be changed and are generated automatically. The only thing that the Data Entry person has to do is to compose the question. The Data Manager, having the required rights, is able to edit the answer field, change the status and result fields, save them in *.pdf* format and if necessary print them out.

- **Ensuring independent double data entry -** The system makes it possible to enter the same CRF by two independent Data Entry Persons. The result is two database tables which can be compared by a third party, using the system compare function. During the comparison process, the system detects the differences and lists them by patients, showing both data values and provides the possibility for correction. The possible corrections are recorded by the *audit trail* function which cannot be switched off. The correction takes place after discussion with the two data entry persons. A new - the third - database table can be created at any time which contains the data identical in both databases. The comparison can be done at any time, so the divergences can be corrected continuously and the final clear database will be available right at the end of the data entry process.

- **Centred management on the server** - The Mythos Admin is a local application running on the server and it makes possible to manage the studies and users. Moreover, it provides a filter function for statistical data of queries, audit trail and errors. These all can be listed and saved in .pdf format and also can be printed out.

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- **Study management – (**Back-up or Restore studies, edit study descriptions) Study data can easily be saved into a separate file protected by individual password. The data manager having the required rights can reload all these data.
- **Admin (Users) -** Creating new users, managing their personal data, assigning them to particular studies with given rights.
- **Query control -** Filtering already existing queries, ordering them into lists, saving them into *.pdf* format and printing them out as it is necessary
- **Error statistics -** According to the data recorded by the audit trail, the system counts and shows the amount of data entered (by users), moreover it indicates the modifications done on them.
- **Audit trail -** Filtering the recorded entries and ordering them into lists, saving them into *.pdf* format and printing them out.

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# INDEPENDENT AUDIT SERVICE (GLP, GCP)

**AdWare Research** conducts independent audits of preclinical (toxicological, safety pharmacological) and clinical trials for pharmaceutical research, development and manufacturing firms. These audits are necessary parts of the registration process for new medical products.

As an independent auditor, **AdWare Research** conducts both trial-specific audits that cover all phases of the clinical trials, and systemic audits according to the **Good Clinical Practice (GCP)** or the **Good Laboratory Practice (GLP)** guidelines.

## THE GCP (GOOD CLINICAL PRACTICE) AUDIT

The "International Conference on Harmonization Harmonized Tripartite Guideline: Good Clinical Practice: Consolidated Guideline [E6] 1996" involves the independent, systematic examination of the data collection, analysis, documentation and other procedures of the organization in order to ensure that they are in compliance with the trial plan that has been approved by regulatory agencies, the standard operating procedures **(SOP)** of the organization, and any applicable law or regulation.

In a trial-specific audit, one or more procedures are examined according to the size and scale of the selected trial. The audit includes assessment of the trial plan, the location of the trial, and the procedures for data processing. The trial plan, patient data **CRF** (Case Report Form) and final reports are examined to ensure accuracy and consistency.

In a systemic audit, the **AdWare Research Development & Consulting Ltd.** conducts an assessment of the organization to determine whether it meets the requirements of the **GCP** or **GLP** and applicable laws or regulations. We examine the system for proper planning, supervision, and documentation necessary to ensure that the trials are conducted according to the **SOPs.**

## THE GLP (GOOD LABORATORY PRACTICE) AUDIT

The **Development & Consulting Ltd.** makes the investigations according to the 9/2001.(III.30.) EüM-FVM on "Good Laboratory Practice and its control" regulation and the OECD Principles of Good Laboratory Practices [ENV/MC/CHEM(98)17] for the following purposes::

1. **Control of one particular trial**
    - Audit of the study plan
    - The places (according to the plan) in order to check whether the trials are taking place according to the GLP regulations. The auditors have to make sure that the study plan and the standard operational procedures (SOPs) are available for the participants and the trial is being accordingly.
    - The audit of the final report in order to check if it contains the required methods' detailed prescription and whether the results are based on raw data and observation.

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- According to the final report a signed statement should be made which contains the type, date, phases of the audit and the date when the report was sent to the management, the study director and local study director (if there is any). The statement should contain that the final report is based on raw data.

**2. Control of a particular laboratory**

The audit of a particular place / laboratory means an investigation to supervise whether the laboratory meets the requirements of the GLP or not.

**3. Control the methods and procedures in a particular laboratory**

Our services are inspected by the *National Pharmacological Institution (OGYI)*

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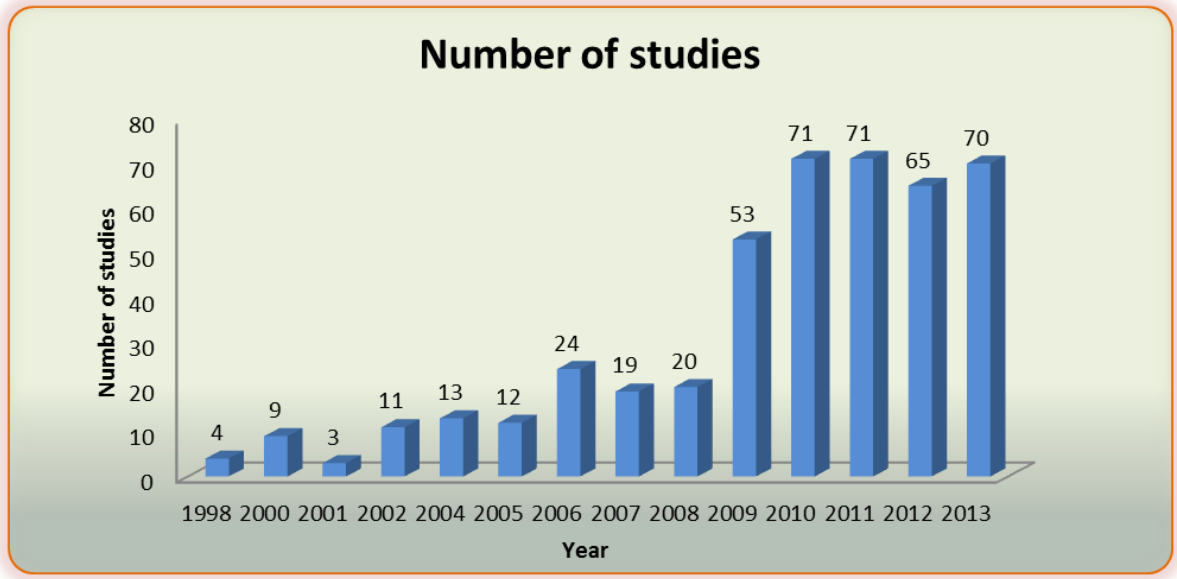
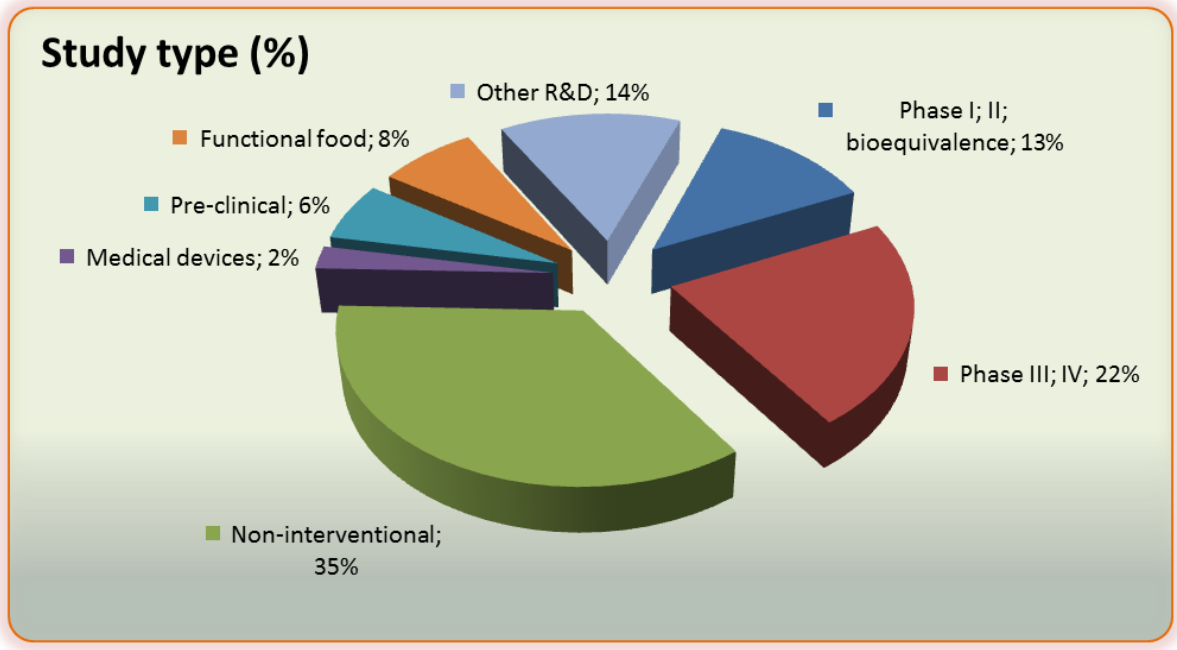
## REFERENCES



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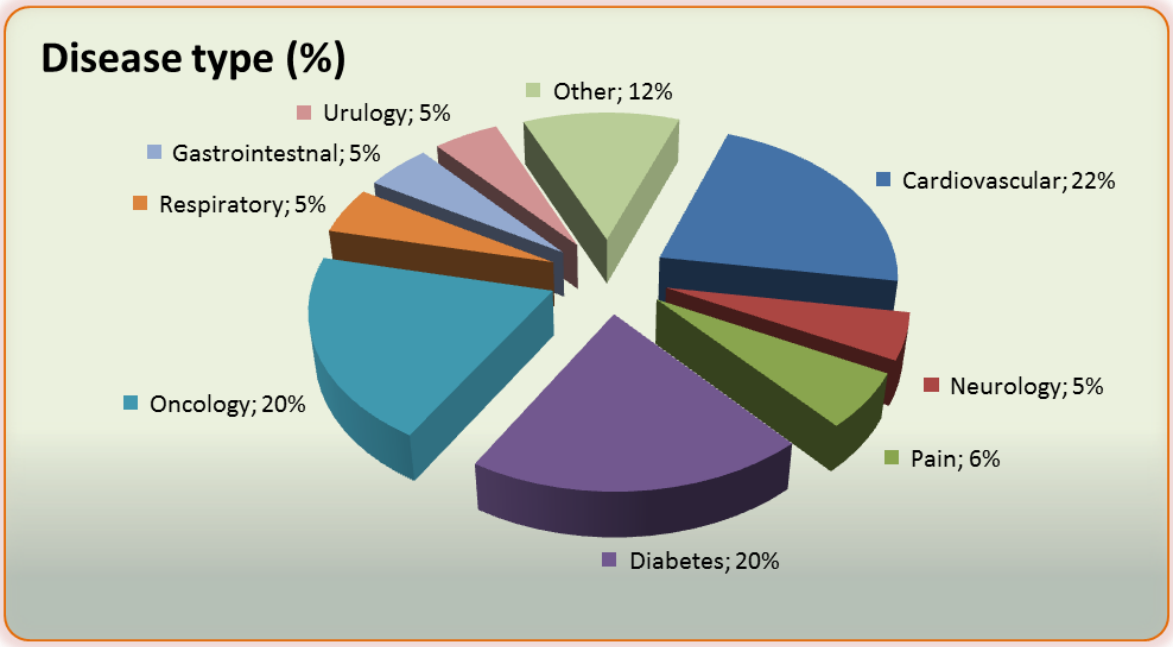


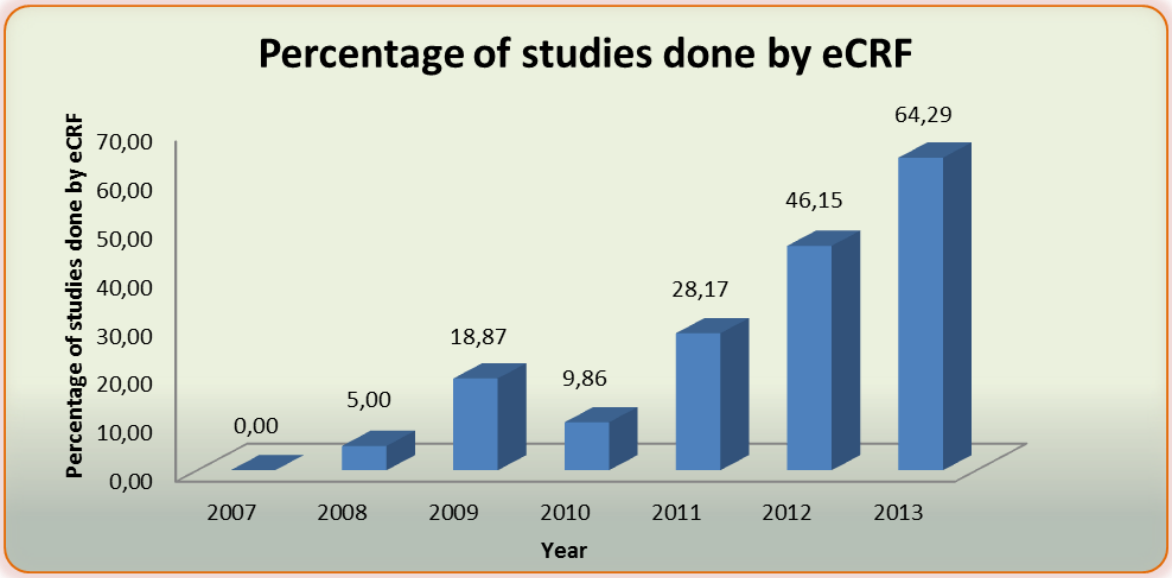

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**They have already chosen AdWare**

| | |
|---|---|
| ACPS - Applied Clinical Pharmacology Services | MEDIX Clinical Services & Consulting Ltd., |
| ADEXGO Ltd | Merck Sharp & Dohme Ltd. |
| Alma Mater Studiorum - Università di Bologna | N-GENE Ltd. |
| AMGEN Ltd. | Novartis Hungary Ltd. |
| AURICOOP Ltd. | Óbuda Healthcare Centre |
| Bayer Ltd. | Periderm 2003 Ltd. |
| BIOGAL-TEVA Plc. | Richter Gedeon Plc. |
| Biosystems International Ltd. | ROCHE Hungary Ltd. |
| Chiesi Hungary Ltd. | Rytmion |
| CHINOIN Plc | Sanofi-Aventis Plc., |
| Copharm Ltd. | Sanofi-Synthelabo Plc. |
| CORTEX CPS. Ltd. | Semmelweis University |
| Diagnosticum Plc. | SERVIER Hungary Ltd. |
| DRC Ltd. | Szegedi Invazív Kardiológiai Kht. |
| EGIS Plc | Szent István University |
| Extractum Pharma Plc. | Szent Laszlo Hospital |
| Experimetria Ltd. | Syncro Ltd. |
| HEMOREX Co. | TARKI Foundation |
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| Immunal Ltd.. | UCB |
| Lavet Pharmaceuticals | Zelion Pharma Ltd., Budapest |
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