



# **ClinResearch**

Institute for Monitoring . Data Management . Biometrics and Medical Writing

## **Adaptive Trials**

International Full Service CRO with  
Core Competence in Adaptive Trials

# ClinResearch - International Full Service CRO with Core Competence in Adaptive Trials

*Adaptive design methods - Revolution in pharmaceutical research and development*

In 1999 **ClinResearch** was founded as a full service provider for clinical studies phase II to IV and post marketing surveillances offering project management, clinical monitoring, data management, statistical consulting & programming, and medical writing.

ClinResearch is located in Cologne, Germany (headquarter) and has subsidiaries in Moscow (Russia), Kiev (Ukraine), San Diego (USA) and Sydney (Australia).



**ClinResearch** is the CRO with the most experience worldwide in the planning and conduction of adaptive designed clinical trials. Through our sister company **ADDPLAN GmbH**, we contribute to the development of the adaptive design methodology. **ADDPLAN** is the leading technology provider in the area of adaptive design software.

The FDA "Draft Guidance on Adaptive Design for Clinical Trials for Drugs and Biologics" defines an adaptive design clinical study as a study that includes a prospectively planned opportunity for modification of one or more specific aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study.

*"The major focus of this guidance is adequate and well-controlled effectiveness (A&WC) studies intended to provide substantial evidence of effectiveness required by law to support a conclusion that a drug is effective."*

## **Benefits of adaptive trials as per guidance:**

- Provides the same information more efficiently
- Increases the likelihood of success on the study objective
- Yields improved understanding of the treatment's effect
- Decreases cost and time without decreasing the informativeness of a study
- Reduces time and resources

This type of trial provides an essential innovation in moving products through the clinical development.

# Bringing together validated expertise, tools and systems ClinResearch offers:

## Statistical Services

### Statistical Section of Study Protocol

According to FDA Guidance, the protocol should contain:

- *“A complete description of all the objectives and design features of the adaptive design, including each of the possible adaptations envisioned the assumptions made in the study design with regard to these adaptations ...”*
- *“A summary of each adaptation and its impact upon critical statistical issues such as hypotheses tested, Type I errors, power for each of the hypotheses, parameter estimates and confidence intervals, sample size”*
- *“Computer simulations intended to characterize and quantify the level of statistical uncertainty in each adaptation and its impact on the Type I error, study power or bias ...”*

**ClinResearch** has been performing adaptive designed trials since its foundation, and has always been one of the first to bring new developments in adaptive theory into practice. We are prepared to deliver the statistical sections for the protocol of your adaptive trial.

Interaction with a broad spectrum of sponsors keeps our mind open for a broad spectrum of adaptive ideas.

**ADDPLAN 5 MC** features an extensive simulation module with a wide variety of options on study design, dose-response relationship, treatment arm selection procedures and sample size adjustment.

Results are given in formats which allow easy integration into the study protocol.

## Interim Analysis - ClinResearch Services

- Continuous adaptive monitoring
- Continuous query generation
- Continuous medical coding
- Statistical programming
  - Loading of current data set
  - Programming of mock-tables and listings
  - Preparation of SAS programs for determination of protocol deviations
- Initiation and loading of snapshot of current data
- Generation and review of blinded and unblinded analysis
- Preparation of Statistical Analysis Plan
- Preparation of Biostatistical Report and forwarding to all members of the DMC
- Real-time access to interim data (interim reports can be provided to the DMC within 3 working days after Database lock)

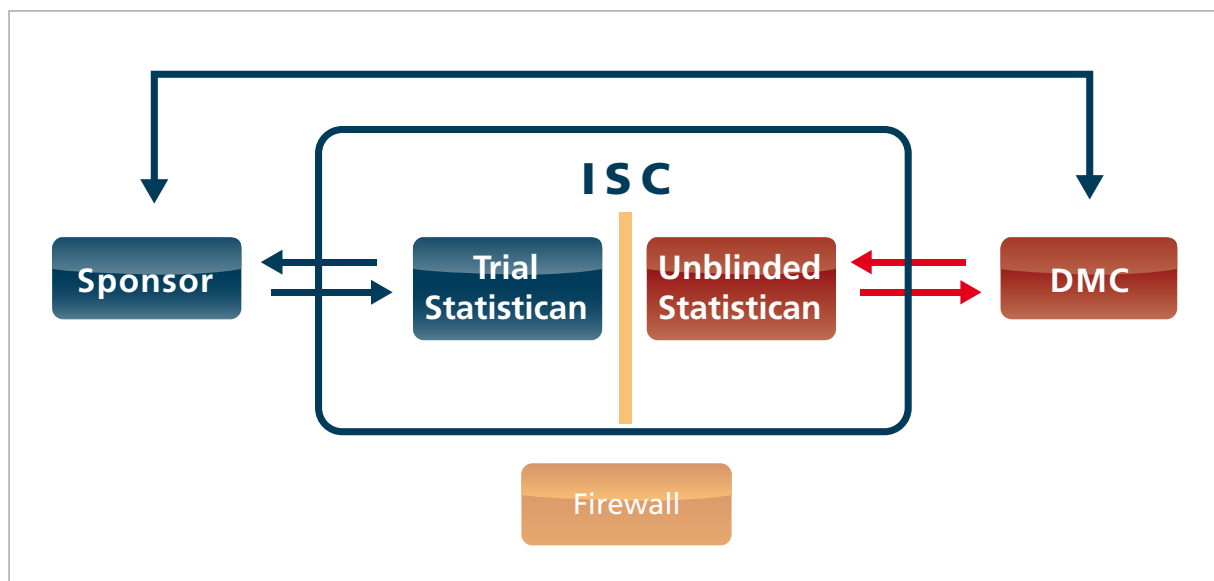
## Interim Analysis - Interaction with DMC

FDA Guidance requires SOPs that define who will implement the interim analysis and adaptation plan and all monitoring and related procedures for accomplishing the implementation.

*“Protecting study blinding is particularly important to avoid the introduction of bias in the study conduct and to maintain confidence in the validity of the study’s result.”*

**ClinResearch** has developed SOPs for interim analysis and unblinding, as well as for communication/management of DMCs/DSMBs in a secure firewalled setting.

**ClinResearch** offers an efficient handling of unblinded data as an Independent Statistical Center (ISC).



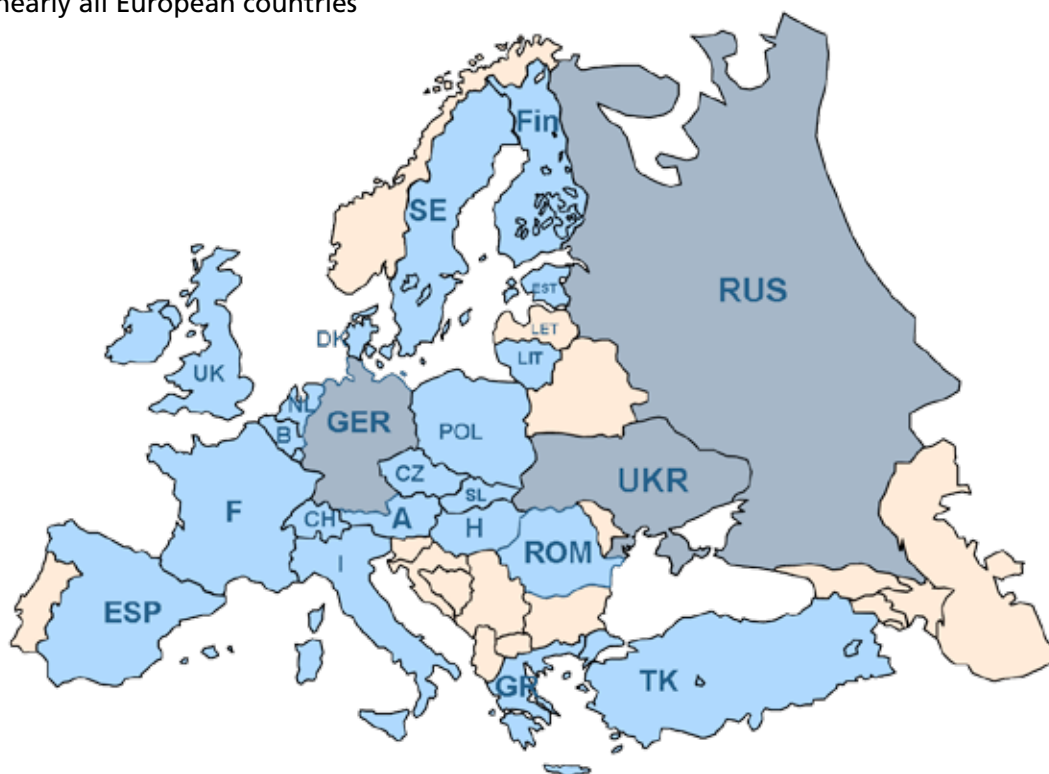
*“An independent, nonsponsor-controlled Data Monitoring Committee (DMC) is an inherent part of the group sequential method’s protection of study integrity. The role of managing study conduct and addressing unexpected study issues is a responsibility that is separate and distinct from the role a DMC will have if it is used to implement a prospective adaptation plan. Because a DMC is unblinded to interim study results, it can help to implement the adaptation decision according to the prospective adaptation algorithm (...).”*

### **ClinResearch DMC Services include:**

- Providing recommendations for DMC members
- Contacting DMC members and organizing DMC meetings
- Providing statistical experts to the DMC
- Establishing DMC SOPs
- Preparing draft DMC charters for review by the Sponsor and DMC members
- Finalizing DMC charter when authorized by the Sponsor and all DMC members
- Providing statistical advice with regard to study design adaptations based on the results of the interim analysis

## Global Project Management and Clinical Monitoring

- Dedicated team of Project Managers and CRAs for each study
- Regulatory services in all European countries
- Site selection and feasibility in all European countries
- Monitoring of sites all over Europe as well as in the US and Australia with own offices in Moscow (Russia), Kiev (Ukraine), San Diego (USA), and Sydney (Australia) and native speakers of nearly all European countries



### Data Management Service

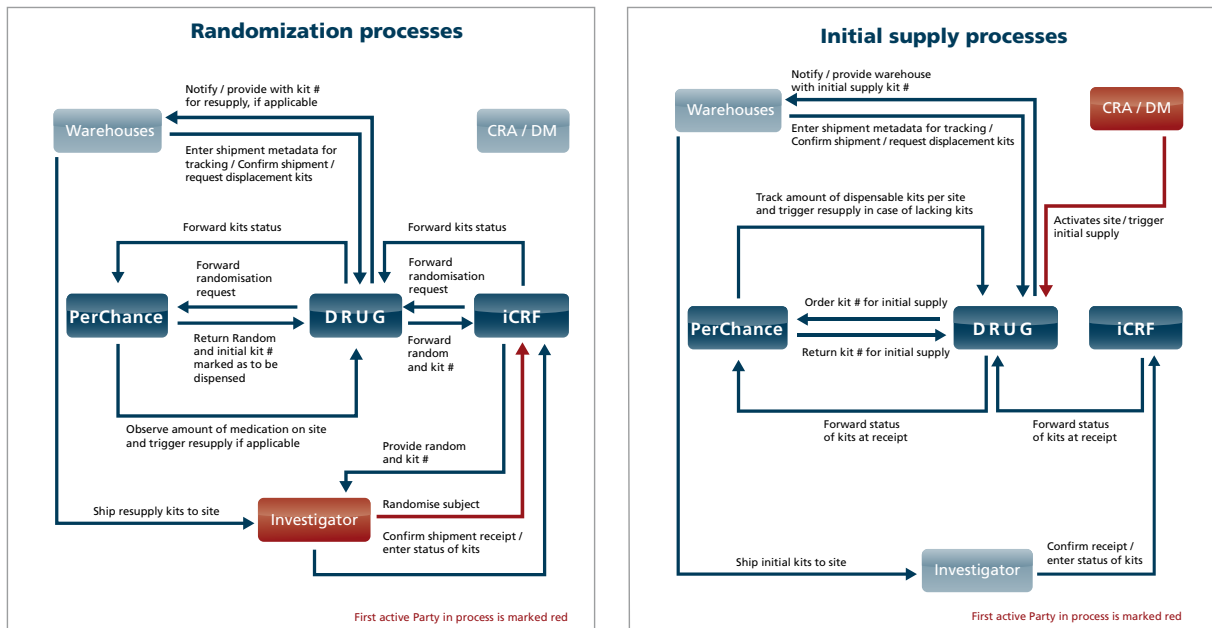
- EDC and paper-based studies
- Preparation and maintenance of Oracle databases
- Double data entry
- Data management plan
- Data validation plan
- Programming of data edit checks
- Query management
- Medical monitoring and coding
- SAE documentation and reconciliation
- **Database soft close for adaptive interim analysis within 3 days after last patient out**

### Data Management Concept

- Efficient teams with clear responsibilities
- Highly flexible
- Sponsor focused
- Associated CDISC member; preparation of data sets according to CDISC standards
- User-friendly, web-based, 21CFR11 compliant clinical data management system including electronic data capture, validated according to GAMP requirements
- **Parallel streamlined processes delivering interim results within shortest timelines**

## On top services for clinical trials:

Our EDC/IWRS systems were specifically designed to support trials with adaptive interim analyses, including management of clinical drug supplies.



### iCRF - ClinResearch's very own data management system

Validation and documentation according to GAMP 5 and 21 CFR Part 11

- Seamless integration of medical coding → fast coding during study
- Query management online and offline → fast data cleaning in parallel to data entry
- Direct data access for statistician → fast statistical evaluation for interim analysis

### DRUG - Drug supply and Randomization Utility Group

The tool provides all drug supply management functionalities, including:

- Management and tracking of medication
- Monitoring of related workflows
- Notification of assigned staff for defined process milestones

### PerChance - Web Randomization Software

This software is used for:

- Randomization
- Medication kit management
- Emergency unblinding

The consistent separation of **PerChance**, dealing with unblinded data (randomization list, mapping of medication kit and treatment group), and **DRUG** ensures that all involved staff is blinded throughout the entire study process.

**ClinResearch offers extensive experience and expertise in the implementation and realization of adaptive designs.**

## Offices

### **ClinResearch GmbH**

#### **Head Office**

Dr. Michael Fischer  
Reinhard Eisebitt  
Managing Direction  
Robert-Perthel-Str. 77a  
50739 Cologne, Germany  
Phone: +49 (0) 221 5999-0  
Fax: +49 (0) 221 5999-400  
contact@clinresearch.com

### **ClinResearch GmbH**

#### **Representative Office in Russia**

Piotr Bayakin  
Head of Representative Office  
Varshavskoye shosse 17, bldg. 1  
117105 Moscow, Russia  
Email: rus@clinresearch.com  
Phone: +7 (0) 495 788 9807  
Fax: +7 (0) 495 788 9817

### **ClinResearch GmbH**

#### **Representative Office in Ukraine**

Dr. Oleksandr Rudovskyi, MD  
Head of Representative Office  
10, Muzeinyi provulok, office 301  
01001 Kiev, Ukraine  
Email: ukr@clinresearch.com  
Phone: +38 (0) 44253 57 37 / 94  
Fax: +38 (0) 44 253 58 31

### **ClinResearch CLL**

Joachim Vollmar  
Managing Director  
3550 General Atomics, M/S 02-422  
CA San Diego 92121, USA  
Email: vollmar@clinresearch.com  
Phone: +1 (858) 909-5745  
Fax: +1 (858) 452-2002

### **ClinResearch Australia PTY Limited**

Janice Labedzki  
Suite 24.05, Quattro Corporate  
4 Daydream Street  
Warriewood NSW 2102, Australia  
Email: aus@clinresearch.com  
Phone: +61 (0) 2 9979 9882  
Fax: +61 (0) 2 9979 5339

# ClinResearch

For more information  
please contact us  
or visit our websites:  
[www.clinresearch.com](http://www.clinresearch.com)  
[www.addplan.com](http://www.addplan.com)

Head Office, Cologne:  
ClinResearch GmbH  
Robert-Perthel-Str. 77a  
50739 Koeln, Germany

Phone: +49.221.5999-0  
Fax: +49.221.5999-400  
[contact@clinresearch.com](mailto:contact@clinresearch.com)