ONKOLOGIE

Supplement 6, Vol. 26,
October 2003

Standard Operating Procedures for Clinical Trials of the CESAR Central European Society for Anticancer Drug Research – EWIV

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Inventory of Current Standard Operating Procedures (SOPs)

SOP no.	SOP title[a]	Current version[b]
01	Clinical Investigations in CESAR	01: 28.06.2001
02	Evaluation and Selection of a Clinical Trial Proposal for CESAR	01: 28.06.2001
03	Preparation and Structure of Trial Protocols	01: 28.06.2001
04	Data Collection Forms (Case Report Forms)	01: 28.06.2001
05	Patient Information and Informed Consent	01: 28.06.2001
06	Selecting the Participating Centers and Activation of a Trial	01: 28.06.2001
07	Data Flow, Monitoring, and Archiving	01: 28.06.2001
07a	Monitoring of a Trial under CESAR Responsibility	01: 28.06.2003
08	Reporting of Adverse Events	01: 28.06.2001
09	Statistical Design and Analysis	01: 28.06.2001
10	Study Report and Publication	01: 28.06.2001
11	Quality Assurance	01: 28.06.2001
12	Validation of Bioanalytical Methods	01: 15.11.2002
13	Pharmacokinetic Data Analysis	01: 15.11.2002
14	Population Pharmacokinetic Analysis	01: 20.06.2003

[a] Primary authorship for individual SOPs: *L. Edler* SOP 10; *U. Jaehde* SOP 12, 13; *R. Port* SOP 14; *H. Sindermann* SOP 1–9, 11.
[b] Valid SOP version as per date of this publication; the homepage of CESAR (*www.cesar-ewiv.org*) should be consulted to verify the version status.

Inventory of SOP attachments

SOP no.	Attachment title	Current version
01	Investigator's Declaration	28.06.2001
	Declaration on the Investigator's Institution	28.06.2001
	Validated Laboratory Normal Ranges	28.06.2001
02	Checklist 2a: Project Evaluation by the Project Review Committee (PRC)	28.06.2001
	Checklist 2b: Vote on Project/Trial Protocol by PRC Members	28.06.2001
	Flow of Information during Protocol Review	14.11.2002
03	Template for the Cover Page of a Clinical Trial Protocol	28.06.2001
	Template for the Synopsis of a Clinical Trial Protocol	28.06.2001
04	Phase I/II Data Collection Forms/Case Reports Forms	28.06.2001
	CTC Criteria; Version 2.0*	30.04.1999
	Current Symptoms/Adverse Event Checklist	28.06.2001
05	Model Patient Information/Informed Consent	28.06.2001
	Template for Patient Information/Informed Consent translated from template of the NCI	28.06.2001

* For guidance on the use of the criteria and notification of recent changes see *http://ctep.info.nih.gov/CTC3/NoM.htm*.

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ADR Adverse Drug Reaction
AE Adverse Event
AIC Akaike Information Criterion
AMG Arzneimittelgesetz (German Drug Law)
ASCII American Standard Code for Information Interchange
AUC Area under the plasma concentration-time curve
AUMC Area under the first moment curve
Basic model A population model that describes all interindividual variability as random (synonym: descriptive model)
BC Biometric Center of CESAR
CE Capillary electrophoresis
CESAR CESAR – Central European Society for Anticancer Drug Research – EWIV
CI Coordinating Investigator (the only investigator determined by CESAR to guide a specific study on behalf of the society)
CE Capillary electrophoresis
CL Total clearance
C_{max} Maximum concentration
C_{min} Minimum concentration after repeated dosing
cov Covariance
Covariate Observable or measurable patient feature like sex, height, smoking habit
CRA Clinical Research Associate
CrCL Creatinine clearance
CRF Case Report Form
C_{ss} Plasma concentration at steady state
CTC Common Toxicity Criteria (NCI)
CV Coefficient of variation
Descriptive model Synonym for: basic model
DLT Dose Limiting Toxicity
EC Ethics Committee
ELS Extended least squares
EMEA European Medicines Evaluation Agency
EWIV Eingetragener Wirtschaftsinteressenverband (European Economic Interest Grouping; EEIG)
Explanatory model A population model that explains interindividual variability partly by differences in covariates like sex, height etc.; contains shift parameters while a basic model does not
F Bioavailability; the fraction of a drug dose which, after extravascular administration, reaches the systemic circulation
f_e Fraction of dose excreted unchanged in urine
f_u Fraction of unbound drug in plasma
GC Gas chromatography
GCP Good Clinical Practice
HPLC High-performance liquid chromatography
ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH-GCP EMEA. Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)
IRB Institutional Review Board
k_a Absorption rate constant
k_M Michaelis-Menten constant
LLOQ Lower limit of quantification
λ_z Terminal elimination rate constant
MTD Maximum Tolerated Dose
NCA Noncompartmental analysis
NCI National Cancer Institute
OLS Ordinary least squares
PBPK Physiologically-based pharmacokinetics
PD Pharmacodynamics
PGDE Pharmacokinetically-guided dose escalation
PI Principal Investigator
PK Pharmacokinetics
Population mean The value of a kinetic parameter that would be expected if there were no interindividual variability (synonym: 'typical value', TV)
Population parameters Population means, shift parameters, interindividual variances (ω^2), residual variance(s) (σ^2)
PRC Project Review Committee
QUAC Quality Assurance Committee
QUC Quality control
RECIST Response Evaluation Criteria in Solid Tumors
SAE Serious Adverse Event
SC Schwarz Criterion
SD Standard deviation
Shift parameter A population parameter that describes a fixed dependence of one of the kinetic parameters (CL, V etc.) on a covariate; examples: a fixed reduction of clearance in females, or a fixed proportionality between drug clearance and individual creatinine clearance
SOP Standard Operating Procedures
Structural model That part of a population model which is adopted before considering variability; it is assumed to hold for all individuals; examples: a linear one-compartment model with first-order absorption, a linear two-compartment model with zero-order input
STS Standard two-stage approach
$t_{1/2\ z}$ Terminal half-life
t_{max} Time of maximum concentration
Typical value Synonym for: population mean
V Volume of distribution
v_{max} Maximum velocity of a Michaelis-Menten process
Vss Volume of distribution at steady-state
VZ Volume of distribution during the terminal phase
WHO World Health Organization
WLS Weighted least squares
ε Residual random deviation from the individual prediction of response (ε is not a population parameter because it varies between observations while its variance is σ^2)
η Individual random deviation from the population mean of a kinetic parameter, or from the individual prediction of this parameter as derived from the population mean and individual covariates (η varies between individuals while its variance is ω^2)
σ^2 Residual random variance (variance of ε)
ω^2 Interindividual random variance (variance of) that is associated with one of the kinetic parameters)

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Preface

The CESAR Central European Society for Anticancer Drug Research – EWIV (CESAR) is a society of scientists in basic research, preclinical oncology, and applied cancer research, sharing as common central mission the development of new antitumoral agents, therapies, and/or therapeutic strategies. Among these areas tumor biology, molecular biology, chemistry, pharmacology, toxicology, clinical pharmacology, biometry, and clinical oncology have to be mentioned in detail. This international society is recruiting its members mainly from the Central European area and is focusing its activities in a common effort of developing new antitumoral substances in Europe. The CESAR is attempting to reflect and represent specifically the geopolitical as well as the sociocultural peculiarities of the Central European region. The CESAR is composed of Central European research associations. The goals of these groups are identical to those of the CESAR. In particular, the CESAR claims to specifically represent Central Europe within a global 'Early Drug Development Network' of Europe. The simplest description of this situation is using the metaphor of a natural ligand (instead of the CESAR) binding with the so far free receptor for new drug development (in Central Europe).

The goal of the CESAR is the development of new antitumoral agents and the clinical testing of new agents and/or antitumoral principles with regard to their effectivity and safety in patients with malignant diseases.

The testing or development of new antitumoral substances has to be based on the scientifically most adequate method, including the pharmacologic expertise and the actual valid state of the art procedures with respect to science, ethics and law. In particular Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP) and Good Clinical Practice (GCP) according to the International Conference on Harmonisation (ICH) have to be considered.

The CESAR has established a permanent committee designated for the task of working out Standard Operating Procedures (SOPs) for the clinical working groups of the society, notably the working groups CESAR Phase-I, CESAR Phase-II and CESAR Phase-III, but also the Working Group on Pharmacology in Oncology and Hematology (CESAR-APOH).

The SOP Committee (SOPC) has undertaken every effort in combining enthusiasm, meticulosity and the wish to produce a useful compendium for clinical researchers in the sense of a codex of how to behave adequately and correctly while performing clinical trials. Thus, the SOPs have been accepted by the CESAR as internal regulation that all members of the CESAR confess to submit to.

Some parts of the SOPs have to be considered as classical parts of such regulation, but representing a very new status including all available and internationally accepted regulations. Especially the 'SOP 12: Validation of Bioanalytical Methods', 'SOP 13: Pharmacokinetic Data Analysis' and 'SOP 14: Population Pharmacokinetic Analysis' represent some rare examples of harmonization in this area which has become of utmost importance to all investigators in the field of new drug development.

We would like to thank all members of the SOPC for their dedication to the creation of these SOPs. In particular we would like to mention the expertise and workload of Dr. Herbert Sindermann. Moreover, we are grateful to Dr. Rüdiger Port and the CESAR-APOH for writing SOPs 12–14.

We wish all clinical investigators in the field of new drug development in oncology that they will find useful information for their daily professional life in this compendium.

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C. Dittrich, President of CESAR

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