

An Investigator's Guide to Ethical Research (2): ICH-GCP in Practice

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Source Documents



Definition: Original documents, data and records (eg hospital notes, clinical charts, laboratory results, pharmacy dispensing records, X-Rays etc).

Source documents may be originals or may be copies, microfiches, photographic negatives once certified as being accurate copies of the original document

ICH-GCP 1.51, 1.52

Case Report Form (CRF)



A printed, optical or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each trial subject

ICH-GCP 1.11

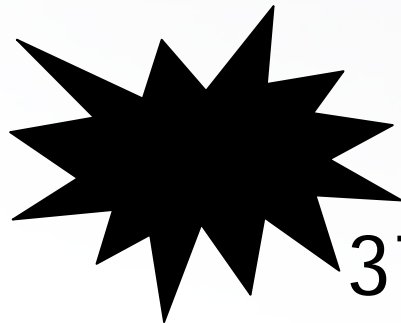
CRF: Investigator responsibility



Ensure the accuracy, completeness, legibility and timeliness of the data in the CRF and all reports

ICH-GCP 4.9.1, 4.9.2

37.4C



37.4C

~~34.7C~~

37.4C

Rod Owen
10/06/2010
Transcription
error

Initial, date (and explain) CRF changes; do **not** obliterate the original entry ICH-GCP 4.9.3

CRFs: Typical data entry errors



Can you spot the error or errors on this page?



E.P.I.C TRIAL	Page No 1
Patient No <u>0023</u>	Patient Initials <u>ABC</u>

INCLUSION CRITERIA

Date 04/05/09

Please tick

	Yes	No
Does the patient have Chronic Myeloid Leukaemia?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Is the patient in the first chronic phase?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Has the patient received Glivec™ for at least 6 months?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Has the Patient achieved complete haematological response (defined as a currently normal Hb, neutrophil and platelet count)	<input type="checkbox"/>	<input type="checkbox"/>
Does the patients CML express the b3a2 BCR-ABL fusion junction ?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Is the patient HLA – A3, -B8 or –A2 positive ?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Is the patient aged 18 or over ?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Have female patients of child bearing age, produced a negative pregnancy test in the last 2 weeks ?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Has the patient given written consent to participate ?	<input checked="" type="checkbox"/>	<input type="checkbox"/>

*** If any question above answered 'no' do not enter patient in trial ***

CRFs: Typical data entry errors



How about this one?



E.P.I.C TRIAL	Page No 9
Patient No <u>0023</u>	Patient Initials <u>ABC</u>

Week 1

Baseline temperature 36.4 °c Pulse 69 bpm 120/70 mmHg

GM-CSF 50mcg/0.1ml given **15** minutes prior to immunisation Yes No

Dose of immunisation 600 mcg

Total volume of immunisation 1.2 mls

Site of Intradermal injection	Right	Left
Suclavicular region	<input type="checkbox"/>	<input type="checkbox"/>
Abdominal wall	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Medial inguinal region of upper thigh	<input type="checkbox"/>	<input type="checkbox"/>

Patient symptoms/effects 60 minutes post injection

Temperature 36.4 °C Pulse 84 bpm Blood Pressure 122/70 mmHg

Injection Site	Discomfort	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
	Swelling	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
	Erythema	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No

If yes to erythema: Diameter _____ cms

Should we really be that bothered?



Safety Reporting



Adverse Event (AE)

Any untoward medical occurrence, including laboratory abnormalities, whether or not considered related to the product, and no matter how minor

ICH-GCP 1.2

* Article 2 (m)

Adverse Drug Reaction (ADR)

Any untoward and unintended medical response to an investigational medicinal product, and related to any dose of the product.

ICH-GCP 1.1

Article 2 (n)

*EU Directives: 2001/20/EC & 2005/28/EC

Safety Reporting



Serious Adverse Event (SAE)

Any untoward medical occurrence that:

results in death

is life threatening (as perceived at the time)

results in persistent disability or incapacity

requires (or prolongs) hospitalisation

is a congenital defect

ICH-GCP 1.50

Article 2 (o)

Safety Reporting



Suspected Unexpected Serious Adverse Reaction (SUSAR)

An adverse reaction, the nature and severity of which is not consistent with the applicable product information (eg Investigator's Brochure if unlicensed; SmPC if licensed)

ICH-GCP 1.60
Article 2 (p)

Adverse Events: Summary



← Unrelated

Related to IMP →



Causal Relationship



Unrelated ...

Unlikely to be related ...

Possibly related ...

Probably related ...

Definitely related ...

} **“Don’t know”**

... to product, device or procedure

'Severity' of Adverse Events



Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

Publish Date: December 12, 2003

Reference

Common Terminology Criteria for Adverse Events a descriptive terminology which can be utilized for Event (AE) reporting. A grading (severity) scale is for each AE term.

Categories and Organization

CATEGORY

CATEGORY is a broad classification of AEs based on etiology and/or pathophysiology. Within each CATEGORY, AEs are listed accompanied by their descriptions of severity.

Adverse Event Terms

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical product or procedure. An AE is a term that is a unique identification of a specific event used for medical reporting and scientific analyses. Each AE term is mapped to a MedDRA term and code. AEs are listed hierarchically within CATEGORIES.

Parent AE Name

The 'PARENT NAME' column is new and it is used to simplify the presentation of AE names on Case Report Forms.

Supra-ordinate Terms

A supra-ordinate term is located within a CATEGORY and is a term based on disease process, signs, symptoms,

or diagnosis. A supra-ordinate term is followed by the word 'Select' and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

REMARK

A 'REMARK' is a clarification of an AE.

ALSO CONSIDER

An 'ALSO CONSIDER' indicates additional AEs that are to be graded if they are clinically significant.

NAVIGATION NOTE

A 'NAVIGATION NOTE' indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the 'NAVIGATION NOTE' states differently.

Grades

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild AE
Grade 2	Moderate AE
Grade 3	Severe AE
Grade 4	Life-threatening or disabling AE
Grade 5	Death related to AE

A Semi-colon indicates 'or' within the description of the AE. An 'Em dash' (—) indicates a grade not available.

Not all Grades are appropriate for all AEs. Therefore, AEs are listed with fewer than five options for selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

The DEATH CATEGORY is new. Only one Supra-ordinate term is listed in this CATEGORY: 'Death not associated with CTCAE term – Select' with 4 AE options: Death due to Disease progression NOS; Multi-organ failure; Sudden Death; and Death Important:

- Grade 5 is the only appropriate Grade
- This AE is to be used in the situation where a death
 - 1. cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
 - 2. cannot be reported within a CTCAE CATEGORY as 'Other (Specify)'


'Severity' of Adverse Events



METABOLIC/LABORATORY							Page 2 of 3
Adverse Event	Short Name	Grade					
		1	2	3	4	5	
Calcium, serum-high (hypercalcemia)	Hypercalcemia	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L Ionized calcium: >ULN – 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L Ionized calcium: >1.5 – 1.6 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L Ionized calcium: >1.6 – 1.8 mmol/L	>13.5 mg/dL >3.4 mmol/L Ionized calcium: >1.8 mmol/L	Death	
Cholesterol, serum-high (hypercholesteremia)	Cholesterol	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L	Death	
CPK (creatine phosphokinase)	CPK	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	Death	
Creatinine	Creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN	Death	
REMARK: Adjust to age-appropriate levels for pediatric patients.							
ALSO CONSIDER: Glomerular filtration rate.							
GGT (γ -Glutamyl transpeptidase)	GGT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	—	
Glomerular filtration rate	GFR	<75 – 50% LLN	<50 – 25% LLN	<25% LLN, chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death	
ALSO CONSIDER: Creatinine.							
Glucose, serum-high (hyperglycemia)	Hyperglycemia	>ULN – 160 mg/dL >ULN – 8.9 mmol/L	>160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL >13.9 – 27.8 mmol/L	>500 mg/dL >27.8 mmol/L or acidosis	Death	
REMARK: Hyperglycemia, in general, is defined as fasting unless otherwise specified in protocol.							
Glucose, serum-low (hypoglycemia)	Hypoglycemia	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L	Death	
Hemoglobinuria	Hemoglobinuria	Present	—	—	—	Death	
Lipase	Lipase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—	

Is it a SUSAR?



Address  http://www.medicines.org.uk/searchresult.aspx?search=caelyx

Medicines.org.uk

Search the site

- Main Menu
 - Home
 - eMC
 - PIL
 - Medicine Guides
 - dm+d/ In-Demand
 - Regulatory News
 - Medicines Compendium Updates
 - Legal
 - Members Area

Search on Medicines.org.uk

You searched for 'caelyx', the following matches have been found.

Results from the eMC

↓ Products - (2 matches found)

Results from dm+d

↓ Actual Medicinal Products - (2 matches found)

Results from the eMC

Products

	Product name
View PIL	Caelyx 2mg/ml concentrate for solution for infusion
View SPD	Caelyx 2mg/ml concentrate for solution for infusion

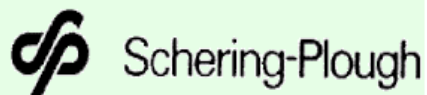
1

Is it a SUSAR? ... SmPC ... 4.8



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Document last updated on the eMC: Mon 11 December 2006

Caelyx 2mg/ml concentrate for solution for infusion

1. NAME OF THE MEDICINAL PRODUCT

Caelyx 2 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Caelyx contains 2 mg/ml doxorubicin hydrochloride in a pegylated liposomal formulation.

Caelyx, a liposome formulation, is doxorubicin hydrochloride encapsulated in liposomes with surface-bound methoxypolyethylene glycol (MPEG). This process is known as pegylation and protects liposomes from detection by the mononuclear phagocyte system (MPS), which increases blood circulation time.

For excipients, see section 6.1.

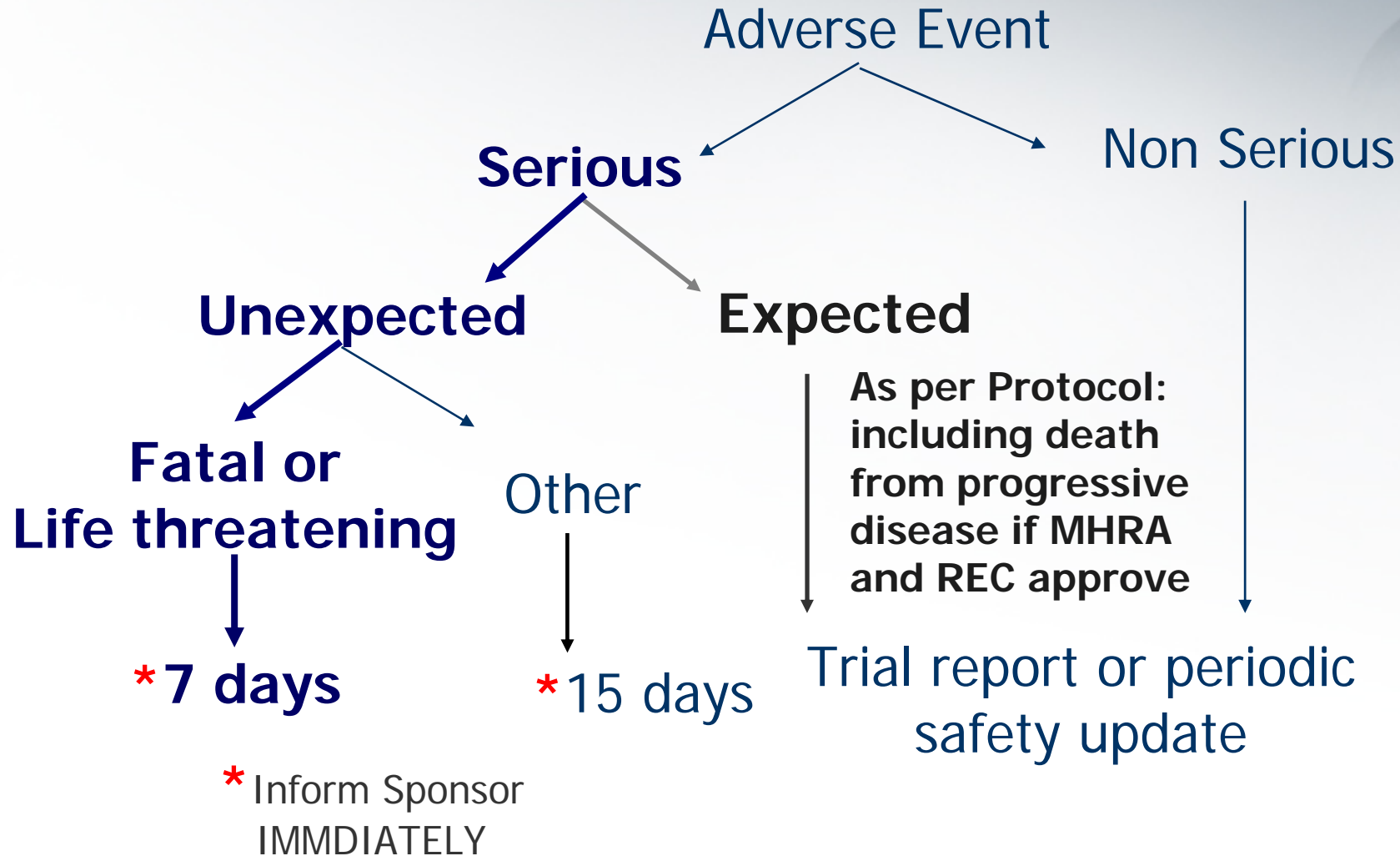
3. PHARMACEUTICAL FORM

Concentrate for solution for infusion

Table 4. Treatment Related Undesirable Effects Reported in Breast Cancer (197-328) and Ovarian Cancer Clinical Trials (50 mg/m² every 4 weeks) (≥ 5 % of Caelyx-treated patients) by Severity, Body System and Preferred Term

AE by body system	Breast Cancer All Severities % n=254	Breast Cancer Grades III/IV % n=254	Ovarian Cancer All Severities % n=512	Ovarian Cancer Grades III/IV % n=512
Blood and lymphatic system disorders				
Leukopaenia	*	*	33	9
Anaemia	5	1	32	6
Neutropaenia	*	*	32	12
Thrombocytopaenia	*	*	11	1
Nervous system disorders				
Paresthesia	*	*	8	< 1
Somnolence	*	*	5	< 1
Respiratory, thoracic and mediastinal				

Adverse Event Reporting



Question 1



A patient gave consent and was entered into a trial yesterday. This morning the patient took the first dose of study medication and felt “severely nauseated” shortly afterwards. The patient was then “violently sick” about 2 hours later.

AE, SAE, NEITHER?

Answer 1



2 AEs: nausea & vomiting
[Temporal separation of two hours]

“Severe” adverse events are not necessarily serious

Question 2



A female patient, who gave consent and agreed to practice adequate contraception in accordance with the study protocol, began treatment with the trial drug three months ago. Last week, the patient reported that she had become pregnant.

AE, SAE or NEITHER?

Answer 2



SAE or AE ... or Neither

ALL pregnancies are usually recorded as SAEs or AEs. This is the convention. However, unless the Investigator believes there may be a **drug-drug interaction** with a contraceptive drug, it should **not** be reported as an (S)AE for licensing.

NOTE: A Report of In Utero Drug Exposure (RIUDE)* **must** be completed for all pregnancies and sent to the MHRA. The Sponsor **must** follow each pregnancy to term, and report outcome to MHRA (even if birth & baby “normal”).

*Clinical Trial Pregnancy Reporting Form

Question 3



A patient entered a 6-week study comparing nicotine patch and nicotine patch plus weekly counselling for 'initial-phase' smoking cessation. One week after consenting to take part in the trial, the patient underwent elective repair of a hernia. The operation was planned to take place in eight weeks time (ie after the study) but a cancellation created the opportunity for earlier surgery, which the patient gratefully accepted.

AE, SAE, NEITHER?

Answer 3



NEITHER

The surgical repair of the patient's hernia was a planned, elective procedure; the altered date makes no difference

(The patient's case notes should show that diagnosis and schedule for surgery pre-dated trial entry ... in compliance with **ICH-GCP**)

Question 4



A patient with advanced malignancy consents to take part in pilot study of a new, patient operated device for delivering pain relief medication, and continues to receive all other medications as per the Trust's "standard practice" in Palliative Care. During the planned 3-week study, the patient dies from disease progression.

AE, SAE, NEITHER?

Answer 4



SAE

Although death may well be considered inevitable for a patient with advanced cancer, and who is receiving palliative care, death is **ALWAYS** an SAE

NB: If stated in Protocol, such SAEs need not be reported using the “expedited” procedure provided MHRA and MREC have agreed to an alternative reporting format

... Seriously - if in doubt, call!

