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## THE PHARMACY AND ENFORCEMENT DIVISION

THE CLINICAL TRIALS DEPARTMENT  
**PROCEDURE FOR**  
**REPORTING AND FOLLOW UP OF REFERENCE**  
**SAFETY INFORMATION DURING THE COURSE OF**  
**CLINICAL TRIALS IN HUMAN SUBJECTS**

### PROCEDURE NUMBER 164/01

EFFECTIVE STARTING

January / 01 / 2019

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Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 2	Procedure Number 164/01

***CONTENT***

List of Abbreviations

Introduction

Procedure Contents

1. Nature
2. Applicable Documents
3. Definitions
4. Responsibility
5. Implementation
  - 5.1 The Principle Investigator
  - 5.2 The Study Sponsor
  - 5.3 The Institutional Helsinki Committee
6. Appendices
  - Appendix 1 – Description of the collection of the information, the classification and the reporting of adverse events
  - Appendix 2 – Form 13 and Form 14
7. Amendments

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 3	Procedure Number 164/01

### ***LIST OF ABBREVIATIONS***

ADR	Adverse Drug Reaction
ADE	Adverse Device Effect
AE	Adverse Event
AR	Adverse Reaction
ATIMP	Advanced Therapy Investigational Medicinal Product
CIOMS	Council for International Organizations of Medical Sciences
CRF/eCRF	Case Report Form / Electronic Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
DSMB/DMC	Data Safety Monitoring Board/ Data Monitoring Committee
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
CVP	Good Vigilance Practice
ICH	International Council for Harmonization (Technical Requirements for Pharmaceuticals for Human Use)
IB	Investigator's Brochure
ISO	International Organization for Standardization
MOH	Ministry of Health
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction

**Print Date June 14, 2018**

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 4	Procedure Number 164/01

USADE      Unanticipated Serous Adverse Device Effect

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 5	Procedure Number 164/01

## ***INTRODUCTION***

Clinical trials in human subjects are necessary for the advancement of health, the introduction of innovative technologies and the promotion of optimal, efficient and safe treatments. The information regarding the safety of a research product is collected in the form of reports during the course of the clinical trial with the purpose of guaranteeing the welfare and safety of those participating in the trial. The follow up for adverse events is crucial and compulsory in accordance with the National Health Ordinance – National Health Regulations (Clinical Trials on Human Beings) [Updated Version], 5741 – 1981, additional legislation relating to the matter, and the international directives and procedures (The Helsinki Declaration and ICH Procedures).

It is the responsibility of all of the entities involved in the initiation, approval and conduction of the clinical trial in human subjects to monitor the adverse events that occur during the course of the trials, to document, assess the extent of the connection to the research product or the trial process, evaluate whether they were foreseeable based on the pre-existing information, and to report them.

Monitoring of the safety reports is a matter of routine and is performed by the bodies that approve the medical products to be marketed in Israel (the Risk Management and Drug Information Department, the Drug Registration Department, the Medical Devices Division and Cosmetics Department). However, products in clinical development stages must be reported to the Clinical Trials Department in addition to the entities involved in conducting the studies. Monitoring of the safety reports allows continuous assessment of the risks of using the research product. Similarly, the process enables examination of the risk–benefit ratio upon reception of new reference safety information, in order to guarantee the safety

**Print Date June 14, 2018**

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 6	Procedure Number 164/01

of the subjects in the present (during the course of the trial) and in the future (continued use and marketing of the research product).

**This procedure replaces Chapter 13 of Procedure 14 of the Pharmacy and Enforcement Division** (The Procedure for Clinical Trials in Human Subjects, Edition 2, 5776 - 2016).

The Director General (defined below in Section 5 of the “Definitions” chapter) may approve a change or deviation from the Procedure at his discretion, pursuant to the circumstances, after he is persuaded that there is justification for doing so.

The Procedure is published on the website of the Pharmacy and Enforcement Division’s Clinical Trials Department, The Ministry of Health, at: [www.health.gov.il/clincialtrials](http://www.health.gov.il/clincialtrials)

### **Application of the Procedure – January / 01 / 2019**

**General Comment:** This procedure, which is written in masculine form solely for purposes of convenience, is intended for both genders.

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 7	Procedure Number 164/01

## ***1. NATURE***

In this Procedure the guidelines for documentation, monitoring and reporting during the course of clinical trials on human subjects are detailed for

- Serious Adverse Events (SAE) that occur during the course of clinical trials using research products which are preparations, medical devices or advanced therapies, which requiring rapid report.
- Safety updates and additional reference safety information.

## ***2. APPLICABLE DOCUMENTS***

- 2.1 The Patient's Rights Act, 5756 - 1996
- 2.2 The National Health Ordinance [New Version], 1940
- 2.3 The Pharmacists Ordinance [New Version], 5741 - 1981
- 2.4 The Public Health Regulations (Clinical Trials in Human Subjects) 5741 – 1980 and all amendments and addendums thereto
- 2.5 The Pharmacists Regulations (Preparations) [New Version], 5746 - 1986
- 2.6 Guidelines for Clinical Trials in Human Subjects [ Procedure 14 of the updated Pharmacy and Enforcement Division]
- 2.7 Procedure for Monitoring and Control Over Medical Trials in Human Subjects [Procedure 144 of the updated Pharmacy and Enforcement Division]
- 2.8 Procedure for Reporting Adverse Events and New Reference Safety Information [Procedure 6 of the updated Pharmacy and Enforcement Division]
- 2.9 Questions and Answers Document regarding the Report of New Adverse Events and Risk Management Plan [Updated Version]
- 2.10 The Helsinki Declaration [Revised Version]
- 2.11 The International Harmonization Procedure for Good Clinical Practice

**Print Date June 14, 2018**

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 8	Procedure Number 164/01

ICH-GCP (E6), Guideline for Good Clinical Practice

**2.12** The International Harmonization Procedures for Management of Clinical Safety Information

ICH-GCP (E2A-E2F), Pharmacovigilance

**2.13** The International Harmonization Procedure regarding the Structure and Content of Reports within the Framework of Clinical Trials:

ICH-GCP (E3), Structure and Content of Clinical Study Reports

**2.14** The current standard for clinical trials in human subjects using medical devices:  
ISO 14155-1, 14155-2: Clinical Investigation of Medical Devices for Human Subjects

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 9	Procedure Number 164/01

### **3. DEFINITIONS**

#### **1. “Adverse Events in a Clinical Trial”**

- a. An “Adverse Event” (AE)** – An undesirable medical phenomenon suffered by a subject in a clinical trial who is treated with the research product, when a connection between the phenomenon and treatment with the product does not necessarily exist.
- b. A “Serious Adverse Event” (SAE)** – An adverse event that is one of the following:
  - Death
  - Life threatening
  - Leads to hospitalization or prolongation of current hospitalization (for example due to the need for medical intervention, or due to a risk of disability, or due to it being life threatening)
  - Causes disability or serious or prolonged incapacity.
  - Causes fetal death or fetal distress or congenital defect.
- c. An “Adverse Drug Reaction” (ADR)** – An undesirable medical phenomenon suffered by a subject in a clinical trial who is treated with a preparation, when a reasonable or possible circumstantial connection was found between the preparation and the adverse reaction.
- d. An “Adverse Device Effect” (ADE)** – An undesirable medical phenomenon suffered by a subject in a clinical trial during the course of using a medical device, when a reasonable or possible circumstantial connection was found between the medical device and the adverse event. This definition includes reactions caused by a device deficiency.

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 10	Procedure Number 164/01

- e. A **“Suspected Unexpected Serious Adverse Reaction” (SUSAR)** – A serious adverse event whose characteristics, frequency of appearance or severity do not correspond to the information about the **preparation** in the source documents (for example: in the Investigator’s Brochure) and when a reasonable or possible circumstantial connection was found between the preparation and the adverse event.
- f. An **“Unanticipated Serious Adverse Device Effect” (USADE)** – A serious adverse event whose characteristics, frequency of appearance or severity do not correspond to the information about the **device** in the source documents (for example: in the Investigator’s Brochure) and when a reasonable or possible circumstantial connection was found between the device and the adverse event (including events caused by a device deficiency).
2. A **“device deficiency”** – Any incompatibility in the identification, quality, stability, reliability, safety or performances of a trial device, including device malfunction, user errors or incompatibility with the information remitted by the manufacturer.
3. **“Helsinki Committee”** – Hereinafter the Institutional Committee: an independent Committee whose composition, manner of appointment and legal quorum are defined in Schedule Two of the National Health Regulations (Medical Trials in Human Subjects), 5741 – 1981.
4. **“The Director”** – The Director General of the Ministry of Health or whosoever is authorized further to all or part of these Regulations.
5. **“The Director of the Institution”** – The Medical Director or Acting Director of the hospital or medical institution at which the clinical trial is conducted, with regard to all or part of these regulations.

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 11	Procedure Number 164/01

6. **“Data Monitoring Committee / Data Safety Monitoring Board (DSMB/ DMC)”**  
– An independent board of experts external to the trial who assess the trial progress, the reference safety information and if necessary the efficacy indexes of the clinical trial. For the purpose of its activity, the DSMB may review unblinded information (at the patient level or treatment group level) during the course of the clinical trial. Based on this review, the DSMB will recommend the introduction of changes to the trial, the continuation of the trial or closing of the trial. EMA or FDA guidelines may be of assistance in this regard.
7. **“Principle investigator”** – In accordance with Procedure 14 of the Pharmacy and Enforcement Division.
8. **“Sponsor”** – in accordance with Procedure 14 of the Pharmacy and Enforcement Division.
9. **“Sponsor / Investigator”** – In accordance with Procedure 14 of the Pharmacy and Enforcement Division.
10. **“Good Clinical Practices (GCP)”** - Work procedures and methodologies designed to guarantee the well-being, welfare and rights of trial subjects and the quality and reliability of the data collected during clinical trials.
11. **“Good Pharmacovigilance Practices (GVP)”** - Work procedures and methods used to identify, assess, understand and prevent safety events or any problem caused as a result of a procedure in a clinical trial.

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 12	Procedure Number 164/01

- 12. “Research product”** — In accordance with Procedure 14 of the Pharmacy and Enforcement Division.
- 13. “Trial protocol”** - In accordance with Procedure 14 of the Pharmacy and Enforcement Division.
- 14. “Medical record”** – Information pursuant to Section 17 of the Patient’s Rights Act documented by way of registration or photocopy or any other manner, including but not limited to the patient’s medical file in which medical documents regarding the patient are kept..
- 15. “Source data”** – The information in the medical record or study records and reliable copies of clinical findings, diagnoses or other activities performed during the course of a clinical trial necessary for reconstruction and assessment of the trial. The source data is saved in the records as original documents or certified copies.
- 16. “Source documents”** – The original documents, data and records, including hospital records, clinical and administrative reports, laboratory results, memos, subject journals, assessment reports, documentation of dispensation, data from computerized systems (including patients files, x-rays, tests), reliable copies, and records saved at the pharmacy, laboratories and other technical departments involved in the clinical trial.
- 17. “Development Safety Update Report” (DSUR)** – An annual report pertaining to a research product in development stages (as well as registered products in an additional research framework which is not in accordance with the terms of registration). The ICH-E2F international procedure defines the common requirements of the DSUR document. In most cases, the Development

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 13	Procedure Number 164/01

International Birth Date (**DIBD**) serves to determine the start of the annual reporting period.

- 18. “Reference Safety Information” (RSI)** – a document containing reference safety information related to the research product. In most cases, this refers to the Investigator’s Brochure (IB). If the research product is registered in Israel or a recognized country, the Summary of Product Characteristics (SmPC) may serve as the RSI.

#### ***4. RESPONSIBILITY***

**The requirements detailed below are in addition to the reporting obligation determined for each trial in the protocol and in accordance with the international guidelines.**

- The procedure refers to research products that are not registered in the State of Israel (preparations, devices and advanced therapies). This refers to products that are not yet registered or products that were registered but are used in a manner which is different from the registered use, or when the use is for a new indication, or when the use is intended to acquire new data related to the registered use, including but not limited to treatment stages.  
Similarly, adverse events which occurred as a result of **medical procedures** constituting part of the trial plan, including preliminary procedures for administration of the research product, are to be reported.
- Safety reports **for products registered in Israel** (whereby the use of the product is in accordance with the terms of registration) must be sent:

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 14	Procedure Number 164/01

- ◆ To the Department of Risk Management and Pharmaceutical Information for Preparations (including advanced therapies), in accordance with the guidelines of Pharmacy and Enforcement Division **Procedure 6**.
  - ◆ To the Medical Devices Division – for medical devices approved by the Medical Devices Division, in accordance with the Division guidelines.
- Reporting of adverse events during the course of a trial at any medical center is required **within the period of time** from reception of the Director's approval (Form 7) and until after the last subject recruited for the trial at the medical center completes the treatment with the research product within the framework of the trial, unless the trial protocol or the Sponsor's procedures determine otherwise. At times, report is required even before reception of the approval (Form 6, 7 or 8), when the report includes data that has an effect on the safety of the trial subjects.
  - The time frames refer to calendar days and not work days. Therefore, in order that the time frames determined be met, reports will also be accepted in the English language.
  - In the case of trials in which blinding must be maintained, the reports to the Ministry of Health will be sent unblinded. However, blindness will be maintained for the study site (the Investigators and the institutional Committees).
  - Authority delegated to another entity does not release that entity of liability pursuant to the law. The delegator of power will verify that the entity accepting responsibility is qualified to perform the role imposed (education, training and experience), and is acting in accordance with the guidelines.

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 15	Procedure Number 164/01

**4.1** The Principle Investigator will report **to the Sponsor and the Institutional Committee** in accordance with the Sponsor's written guidelines and Section 5.1 in this procedure. In all instances in which term "Investigator" is used, the reference is to the Principle Investigator or to whosoever was delegated authority by the Principle Investigator in writing.

**4.2** The Study Sponsor will report to the **Lead Investigator and to the Ministry of Health**, in accordance with the International Harmonization Procedures and Section 5.2 of this procedure, which defines the local requirements. In all instances in which the term "Sponsor" is used, the reference is to the Trial Sponsor (commercial, investigator, academic or nonprofit sponsor) or to the Sponsor's representative to whom the authority was delegated in a written contract between the parties.

**4.3** The Institutional Helsinki Committee **will report to the Principle Investigator** (regarding the Committee's decisions further to its reports) **and to the Ministry of Health** in accordance with the written guidelines in Section 5.3 of this procedure.

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 16	Procedure Number 164/01

## 5. IMPLEMENTATION

### 5.1 The Chief Investigator

#### 5.1.1 Documentation and Assessment

The Investigator shall record in the medical records all of the adverse events suffered by the subjects during the trial for which he is responsible. The Investigator shall perform an assessment of the seriousness of the event and an assessment of the causality of the possible connection to the research product (or the reference product). The Investigator who performs the medical review will document this in the medical records of each subject (*Source Document*) and in the study records.

The Investigator shall receive the reports from the Sponsor, read them, provide his opinion and forward them, together with his opinion, to the Institutional Committee.

#### 5.1.2 Reporting in the event of death

**5.1.2.1** In the case of a study sponsored by a commercial Sponsor, the Investigator shall report the event that occurred in the study for which he is responsible. The report **to the Sponsor** will be made as soon as possible after the moment the event was brought to the Investigator's attention, or pursuant to the time frame determined by the Sponsor in the protocol and in the Sponsor's procedures (**up to 48 hours**). In parallel, the Investigator will report the death incident within **48 hours** on Form 13 **to the Institutional Helsinki Committee Chairman**.

The Investigator shall report any new data concerning the matter to the Sponsor using *follow-up reports* in accordance with the Sponsor's guidelines. The Sponsor shall receive the report from the Investigator and perform an initial assessment of the possible connection to the research product and assess

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 17	Procedure Number 164/01

whether the event was *expected / anticipated*. The Sponsor will remit his decision regarding the death incident to the Investigator only when it is determined that the case is that of a USADE / SUSAR at his center within **7 days** of the death incident notice.

The Investigator shall forward the Sponsor's decision to the Institutional Committee using Form 13 (or another Sponsor report) immediately after it is determined that the case is that of a USADE / SUSAR. If such a decision was not made within 7 days, the Investigator will document that it was decided that the case was not that of a USADE / SUSAR and he will bring this to the attention of the Committee, including his opinion regarding the classification of the event.

**5.1.2.2** In the case of a study sponsored by an Investigator / Academic / Nonprofit Sponsor, the Investigator shall report to the Institutional **Helsinki Committee** within **48 hours** of the moment the event was brought to his attention, in the case of an event involving a subject participating in a clinical trial for which he is responsible. The Investigator shall make his report using Form 13 (including his opinion). It is the responsibility of the Investigator contact the manufacturer or the registration holder of the research product, to report the death incident and to receive the most up to date reference safety information for the research product. This, in order to perform an information-based safety assessment of the possible connection to the research product as well as an assessment regarding whether the event was expected / anticipated.

### **5.1.3 Reporting in the case of a life threatening event**

**5.1.3.1** In the case of a study sponsored by a Commercial Sponsor, the Investigator shall report the event that happened during the trial for which he is responsible.

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 18	Procedure Number 164/01

The report to the **Sponsor** will be made as soon as possible after the Investigator learns of the event, or pursuant to the time frame determined by the Sponsor in the protocol and in the Sponsor's procedures. Similarly, the Investigator will report any new data concerning the matter to the Sponsor using follow-up reports, in accordance with the Sponsor's guidelines. The Sponsor shall receive the report from the Investigator, perform an initial assessment of the seriousness of the event and the possible connection to the research product, and assess whether the event was foreseeable / expected. The Sponsor shall return his decision on the SAE to the Investigator only when it is determined that the case is that of a USADE / SUSAR at his center, within **7 days** of the SAE notice.

The Investigator shall forward the Sponsor's decision to the Institutional Committee using Form 13 (or another Sponsor report) immediately after it is determined that the case is that of a USADE / SUSAR. If such a decision is not received within 7 days, the Investigator will document that it was decided that the case is not that of a USADE / SUSAR and that there is therefore no need to report to the Committee. The Investigator may report to the Committee if in his opinion the classification was changed.

**5.1.3.2** Under the sponsorship of an Investigator / Academic / Nonprofit Sponsor, the Investigator will report the event that occurred during the trial for which he is responsible within **7 days** of the moment he learns of the event, to the Institutional **Helsinki Committee**. The Investigator will make his report using Form 13 (including his opinion). The Investigator must report any new data concerning the event to the Helsinki Committee using follow-up reports. It is the responsibility of the Investigator to contact the manufacturer or the registration holder of the research product to report the adverse event and to receive the most up to date reference safety information for the research

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 19	Procedure Number 164/01

product. This, in order to perform an information-based safety assessment of the seriousness of the event and the possible connection to the research product as well as an assessment regarding whether the event was foreseeable / expected.

#### **5.1.4 Reporting A SAE that is not death or which is not life threatening**

**5.1.4.1** In the case of a study sponsored by a commercial Sponsor, the Investigator shall report any SAE that occurs in a trial for which he is responsible to the **Sponsor**. The report will be made as soon as possible after the Investigator learns of the event or pursuant to the time frame determined by the Sponsor in the protocol and in the Sponsor's procedures. The Sponsor shall receive the report from the Investigator and conduct an initial assessment of the seriousness of the event and the possible connection to the research product, as well as an assessment regarding whether the event was expected / anticipated. The Sponsor shall return his decision regarding the SAE to the Investigator only when it is determined that the event was an USADE/ SUSAR at his center within **15 days** of the SAE notice.

The Investigator shall forward the Sponsor's decision to the Institutional Committee using Form 13 (or other report of the Sponsor) immediately after it is determined that the case is that of a USADE / SUSAR. If such a decision is not received within 15 days, the Investigator will document that it was decided that the case was not that of a USADE / SUSAR and that there is therefore no need to report to the Committee. The Investigator may report to the Committee if in his opinion the classification was changed.

**5.1.4.2** In the case of a study sponsored by an Investigator / Academic / Nonprofit Sponsor the Investigator will report any serious adverse event (SAE), including

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 20	Procedure Number 164/01

his opinion, to the chairman of the Helsinki Committee within **15 days** of the moment the event was brought to his attention. The Investigator will make his report using Form 13. The Investigator must report any new data concerning the event to the Helsinki Committee using follow-up reports in accordance with the Sponsor's guidelines. It is the responsibility of the Investigator to contact the manufacturer or the registration holder of the research product, to report the adverse event and to receive the most up to date reference safety information for the research product. This, in order to perform an information-based safety assessment of the seriousness of the event and the possible connection to the research product as well as an assessment regarding whether the event was foreseeable / expected.

### **5.1.5 Additional Reports to the Institutional Committee**

**5.1.5.1 RSI update** (IB or SmPC update) after approval in a recognized country. The updated document shall be sent to the Committee within **15 days** of reception of the information from the Sponsor. This document will be forwarded to the Committee even before approval is received to conduct the trial.

**5.1.5.2 A Notice to the Medical Team** published by the Manufacturer or health authority in a recognized country, or new data published in the **professional medical literature** which has implications for the safety of the research product and use thereof in human subjects. This refers to information which includes any **prohibition, restriction or warning associated with the safety of the trial subjects**. The notice shall be sent within **15 days** of the day the information is received from the Sponsor. This information will be remitted to the Committee even before approval is received to conduct the trial.

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 21	Procedure Number 164/01

**5.1.5.3 The conclusions of the Safety Committee** for a medical trial (DSMB / DMC) in which the decision was made to make modifications to the protocol which affect the safety of the patients or terminate the trial shall be sent within **15 days** of the reception of the information from the Sponsor. This notice will be remitted to the Committee even before approval is received to conduct the trial.

**5.1.5.4 New findings** associated with the conduction of the trial or the development of the research product that are likely to affect the safety of the trial subjects shall be sent within **15 days** of the day the information was received from the Sponsor. For example a significant safety finding in animal trials which have recently been completed (such as: carcinogenicity); lack of efficacy of a research product used to treat a life threatening disease. This information shall be remitted to the Committee even before approval is received to conduct the trial.

**5.1.5.5** The decision in principle made by the **regulatory authority** of a recognized country, referring to the continuation of the trial due to safety concerns, including temporary or absolute termination thereof, as well as a decision to recommence the trial after its termination. The notice will be sent within **7 days** of its reception from the Sponsor.

**5.1.5.6 Periodic line listing** – The report will include a concentrated list of the USADE / SUSAR events at a frequency of at least once every six months. The report will be accompanied by a summary of the main issues that arose regarding the safety of the research product within the time frame described in the report while **maintaining the blindness** of the trial.

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 22	Procedure Number 164/01

**For all of the reports above**, the Investigator will attach a **summary** of the changes and findings regarding the safety issue and the implications thereof on the data to be remitted to the trial subjects (who were already recruited or who are to be recruited). In cases in which the consent form must be updated, the new data will also be attached, to be delivered to the subjects, including time frames and the manner in which the subjects were contacted.

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 23	Procedure Number 164/01

**TABLE 1:** The Investigator SAE Report

Sponsor type	SAE type	Time frame for reporting to the Sponsor	Time frame for reporting to the Committee	Time frame for follow-up reports to the Committee
<b>Commercial</b>	Death	As soon as possible and according to Sponsor 's guidelines [within 48 hours]	Within 48 hours	7 days from the reception of a notification regarding the event at the center
	Life threatening	As soon as possible and according to Sponsor 's guidelines	-	7 days and <u>only</u> when it has been determined that the case is that of a USADE / SUSAR
	An SAE that is not a death or life threatening	As soon as possible and according to Sponsor 's guidelines	-	15 days and <u>only</u> when it has been determined that the case is that of a USADE / SUSAR
<b>Investigator / Academic / Non-profit</b>	Death	-	Within 48 hours	-
	Life threatening	-	7 days	-
	An SAE that is not a death or life threatening	-	15 days	-

**TABLE 2:** Additional safety reports which the Investigator is responsible to report to the Committee

Print Date June 14, 2018

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 24	Procedure Number 164/01

Document / data type	Time frame for reporting to the Committee	Also required before approval?	Additional information
RSI (SmPC or IB) update after approval in a recognized country	15 days	Yes	A summary of the changes
A notice to the medical team or new data published in the professional literature which has implications for the safety of use in human subjects	15 days	Yes	A summary of the safety data
The conclusions of the Safety Committee	15 days	Yes	A summary of the decision
New findings which may affect safety	15 days	Yes	A summary of the safety information
A decision in principle made by the regulatory authority of a recognized country	7 days	No	
Periodic reports (blindness shall be maintained)	Every 6 months	No	

## 5.2 The Study Sponsor

The Sponsor shall act in accordance with the guidelines of the international procedures to continuously assess the safety of the use of the research products and manage the quality of the trials for which he is responsible.

### 5.2.1 Documentation and assessment

Print Date June 14, 2018

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 25	Procedure Number 164/01

The Sponsor shall ensure that there is suitable documentation of the safety events, including the information required to perform an assessment of the severity and the causality of the adverse events. The Sponsor shall perform a seriousness assessment of the event, a causality assessment regarding the possible connection to the research product (or the reference product) and will evaluate whether the event was expected / anticipated in terms of its characteristics, severity and frequency of appearance, based on the pre-existing information. The Sponsor's assessment will be conducted independent of the reporting Investigator's conclusions. The Sponsor shall document his conclusions as well as the Investigator's conclusions even in cases in which they disagree.

## **5.2.2 Reporting a death event or life threatening event**

**5.2.2.1** A (Commercial) Sponsor who receives a report from the Investigator regarding the case and any new information related to the matter through the follow-up reports will assess the seriousness of the event, the possible connection to the research product and whether the event was foreseeable in terms of its characteristics, severity and frequency of appearance, based on the pre-existing data. The Sponsor shall remit his decision regarding a death incident or life threatening incident back **to the Investigator only** when it is determined that is the case is that of a USADE/SUSAR at his center, within a limited period of time of **7 days** (of receiving the notice). In cases in which the consent form must be updated, the new information will also be attached to be remitted to the subjects, including the time frames and the manner in which the subjects were contacted.

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 26	Procedure Number 164/01

In parallel, the Sponsor will report the event to **the Ministry of Health** only if he decides that it is a USADE / SUSAR. The notices regarding USADE/ SUSAR events that occurred at centers in Israel only will be emailed to the 'Clinical Trials Control' inbox: [ct\\_compliance@MOH.GOV.IL](mailto:ct_compliance@MOH.GOV.IL) (the subject of the notice must include: blinded study / non-blinded study, the protocol number, the center in Israel and the date of the report including the month and the year). The information will be sent unblinded. In addition, the notice will include the reason due to which it was decided that the case is that of a USADE/ SUSAR, as well as the Sponsor's decision regarding continuation of the trial and the required amendments to the information remitted to the subjects.

**5.2.2.2** An Investigator / Academic / Nonprofit Sponsor will act in accordance with Section 5.1.2.2.

### **5.2.3 Reporting an SAE that is not a death or life threatening event**

**5.2.3.1** A (Commercial) Sponsor, who receives a report from the Investigator regarding the SAE and any new information concerning the matter through the follow-up reports shall conduct an assessment regarding the seriousness of the event, the possible connection to the research product and whether the event was foreseeable in terms of its characteristics, severity and frequency of appearance based on pre-existing data. The Sponsor will remit his decision regarding the SAE back **to the Investigator** only when it is determined that the case is that of a USADE / SUSAR at his center, within a limited period of time of **15 days** (of reception of the notice pertaining to the SAE). In cases in which the consent form must be updated, the new information will also be attached to be remitted to the subjects, including the time frames and the manner in which the subjects were contacted.

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 27	Procedure Number 164/01

In parallel, the Sponsor shall report the event to **the Ministry of Health** only if he decides that the case is that of a USADE / SUSAR. The notices regarding USADE/ SUSAR events that occurred at centers in Israel only will be emailed to the 'Clinical Trials Control' inbox: [ct\\_compliance@MOH.GOV.IL](mailto:ct_compliance@MOH.GOV.IL) (the subject of the notice: blinded study / non-blinded study, the protocol number, the center in Israel and the date of the report including the month and the year). The body of the notice must include the details of the case and reference the product received by the subject. The information will be sent unblinded. In addition, the notice will include the reason due to which it was decided that the case is that of a USADE / SUSAR, as well as the Sponsor's decision regarding continuation of the trial and the required amendments to the information remitted to the subjects.

**5.2.3.2** An Investigator / Academic / Nonprofit Sponsor will act in accordance with Section 5.1.4.2.

#### **5.2.4 Additional reports to be sent to the Investigator**

**5.2.4.1 RSI update** (IB or SmPC update) after approval in a recognized country. The updated document will be sent within **15 days** of the day of its approval. A summary of safety-related changes as well as the update required in the consent form must be attached. This document will be forwarded to the Investigator even before approval is received to conduct the trial.

**5.2.4.2 A Notice to the Medical Team** published by the Manufacturer or health authority in a recognized country, or new data published in the **professional medical literature** which has implications for the safety of the research product and use thereof in human subjects. This refers to information which includes

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 28	Procedure Number 164/01

any safety-related **prohibition, restriction or warning**. The notice will be sent within **15 days** of the day the information is received from the Sponsor. A summary of the information regarding the safety issue and the required update to the consent form must be attached. This information will be remitted to the Investigator even before approval is received to conduct the trial.

**5.2.4.3 The conclusions of the Safety Committee** for the clinical trial (DSMB / DMC) the decision was made to make modifications to the protocol which affect the safety of the patients or terminate the trial. The summary will be sent within **15 days** of reception of the Committee's decision. This notice will be remitted to the Investigator even before approval is received to conduct the trial.

**5.2.4.4 New findings** associated with the conduction of the trial or the development of the research product that are likely to affect the safety of the trial subjects shall be sent within **15 days** of the day the information summary was received by the Sponsor. For example, a significant safety finding in animal trials which have recently been completed (such as: carcinogenicity); lack of efficacy of a research product used to treat a life threatening disease. This information shall be remitted to the Investigator even before approval is received to conduct the trial.

**5.2.4.5** A decision in principle made by the **regulatory authority** of a recognized country, referring to the continuation of the trial due to safety concerns, including temporary or absolute termination thereof, as well as a decision to recommence the trial after its termination. The notice will be sent within **7 days** of its reception from the Sponsor.

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 29	Procedure Number 164/01

**5.2.4.6 Periodic line listing** – The report will include a concentrated list of the USADE / SUSAR events at a frequency of at least once every six months. The report will be accompanied by a **summary** of the main issues that arose regarding the safety of the research product within the time frame described in the report while **maintaining the blindness of the trial**.

### **5.2.5 Additional reports to be sent to The Ministry Of Health**

Reports for trials have been approved or that are in the process of approval by the Clinical Trials Department.

**5.2.5.1** All of the reports detailed in Sections 5.2.4.1 through to 5.2.4.5 above, and within the same time frames. The notice, which includes the document, will be sent to the email of the unit that handled the approval of the application (the message subject must include: the Ministry of Health application number, the protocol number and the date of the report, including the month and year). In the body of the notice a summary of the changes and the safety findings, as well as their implications in terms of the information to be remitted to the trial subjects (those who have been recruited or those who are to be recruited), must be added to the body of the notice. .

**5.2.5.2 Safety addenda** – Safety updates for the Investigator’s Brochure for studies that have not yet received approval from the Clinical Trials Department (Form 8) shall be sent to the **Ministry of Health** within **15 days** of the final approval of the document.

The notice, which must include the revised document, shall be emailed to the unit that handled the approval of the application (the message subject must include: the Ministry of Health application number, the protocol number and the Safety addenda).

**Print Date June 14, 2018**

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 30	Procedure Number 164/01

**5.2.5.3 An annual report summary (DSUR)**, to include the Executive Summary and conclusions (unblinded), must be emailed **to the Ministry of Health** within **60 days** of its being issued, to: [dsur@MOH.GOV.IL](mailto:dsur@MOH.GOV.IL) 'Annual Safety Reports' (the message subject must include: the Ministry of Health application number, the protocol number and the date of report, including the month and year).

The DSUR will be sent once a year, in accordance with the Harmonization procedures guidelines. The **complete** annual report will only be sent upon the request of the Ministry.

**TABLE 3:** The Sponsor's report of SUADE / SUSAR decisions at Israeli institutions

Sponsor	The type of SAE <u>determined</u> to be a USADE / SUSAR	Time frame for reporting to the Investigator	Time frame for reporting to the MOH	MOH email address for reports
<b>Commercial</b>	Death / life Threatening	Within 7 days of the Investigator's report	Within 7 days of the Investigator's report in Israel	'Clinical Trials Control': <a href="mailto:ct_compliance@MOH.GOV.IL">ct_compliance@MOH.GOV.IL</a>
	An SAE which is not death or life threatening	Within 15 days of the Investigator's report	Within 15 days of the Investigator's report in Israel	'Clinical Trials Control': <a href="mailto:ct_compliance@MOH.GOV.IL">ct_compliance@MOH.GOV.IL</a>

**TABLE 4:** Additional safety reports to be sent to the Ministry of Health (trials that have been approved or are in the process of approval by the Clinical Trials Department).

Document / information type	Time frame for reporting to the MOH	MOH email address for reports
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Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 31	Procedure Number 164/01

The reports detailed in Sections 5.2.4.1 to 5.2.4.5	In parallel to the report to Investigators (15 days or 7 days for Section 5.2.4.5)	‘The Clinical Trials Department - Drugs’ <a href="mailto:clinicaltrials.pharm@MOH.HEALTH.GOV.IL">clinicaltrials.pharm@MOH.HEALTH.GOV.IL</a> Or ‘Clinical Trials - Medical Devices’ <a href="mailto:Clinical.trials.devices.@MOH.HEALTH.GOV.IL">Clinical.trials.devices.@MOH.HEALTH.GOV.IL</a>
Safety updates to the Investigator’s Brochure (Safety addenda)	15 days	‘The Clinical Trials Department - Drugs’ <a href="mailto:clinicaltrials.pharm@MOH.HEALTH.GOV.IL">clinicaltrials.pharm@MOH.HEALTH.GOV.IL</a> Or ‘Clinical Trials - Medical Devices’ <a href="mailto:Clinical.trials.devices.@MOH.HEALTH.GOV.IL">Clinical.trials.devices.@MOH.HEALTH.GOV.IL</a>
Periodic report summary (DSUR)	60 days	‘Annual Safety Reports’ <a href="mailto:dsur@MOH.GOV.IL">dsur@MOH.GOV.IL</a>

### 5.3 The Institutional Helsinki Committee

#### 5.3.1 Documentation of Assessments and Decisions

The Helsinki Committee will examine and assess the information received in the reference safety reports with regard to the continuation of the trials approved by it. The Committee will save the reports received and all of the decisions related to all trials that fall under its responsibility. The Institutional Helsinki Committee will operate pursuant to the work procedure regulating the reporting requirements, documentation of reports from Investigators, decisions made by the Committee (or a Committee representative) and notice of these decisions to the Principle Investigator and to the Ministry of Health. This procedure will be available to the institution employees who hold positions related to the conduction of clinical trials, the studies Sponsors or their representatives, and the Ministry of Health. The Committee will permit the reception of reports on

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 32	Procedure Number 164/01

the Sponsor's report forms in the English language (without the use of Form 13).

The reports received from the Investigator have an effect on safety and the Committee is therefore responsible for examination of the risk–benefit ratio upon reception of the new information. The Committee will examine the information received and its implications for the safety of the trial subjects and the continuation of the trial as well as the implications for the informed consent process. If the consent form requires updating, the urgency and necessity of updating the information remitted to the subjects must be examined.

For example, in the event that the risk to the subjects' safety increases, the information which impacts their health must be brought to their attention and it must be verified that they have a way to report in an emergency. When a quick update is required, it may be remitted in a document containing the main points of the information and the subjects may be contacted verbally, without waiting for the informed consent form to be updated. However, in cases in which the update is not urgent (medical or autonomous, such that it has no effect on the decision whether to continue the trial), it is possible to wait until a new copy of the consent form or the revised translated document is received.

The Committee shall decide whether to continue the trial and determine the urgency and manner of notification of the subjects participating in the trial, and a notice be sent to the **Investigator** including the time frames for execution of the decision.

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 33	Procedure Number 164/01

The Investigator may report to and consult with the Committee in cases in which the Sponsor determined that the SAE that occurred which falls under his responsibility will not be classified as a SUSAR and the Investigator does not agree with this determination. The Committee may receive additional information from the Sponsor and, accordingly, decide to continue the trial approved by it. Notice to the Ministry of Health will only be sent in case of a change in the trial status.

### 5.3.2 Reporting a death

**5.3.2.1** There is no connection / there is a low probability of a connection to the research product or the study process. The Helsinki Committee Chairman who receives notice of the death will evaluate the case; and if he concludes that the death is unrelated, or that the probability is low that the death is related to the use of the research product or to the study process (for example, in cases of disease progression), he will document his decision using Form 13. The form will be sent **to the Investigator** and will include a decision to continue the trial.

**5.3.2.2** There is a connection / a connection is highly probable / it is not possible to rule out a connection to the research product or the study process. If the Committee Chairman is of the opinion that there is a connection or that a connection is highly probable or that it is not possible to rule out a connection between the death and the use of the research product or the study process, he will immediately notify the Director of the Medical Institution that he must appoint an investigative team (it is possible to consult with the institutional Risk Management Unit and with the Principle Investigator). In parallel, he may order that recruitment to the trial be halted until the completion of the investigation. If the decision is made to halt recruitment, the implications thereof for the

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 34	Procedure Number 164/01

subjects must be addressed. The investigative team shall discuss the case within **14 days** of the date that the event was brought to the attention of the Director of the Medical Institution, and decide whether there is or there is not a connection between the event and the use of the research product. The report prepared by the investigative team as well as the Investigator's opinion (the Sponsor's decision will only be sent if it was determined that the case is that of a USADE / SUSAR) will be discussed by the Institutional Helsinki Committee at its next meeting or by a limited panel defined in the Committee's work procedure. The Committee will decide whether to continue the trial / halt recruitment of new subjects for the trial / discontinue the trial / other decision).

The discussion and the decision shall be documented using Form 14 (Part B) and brought to the attention of **the Investigator and the Director** of the Medical Institution. Notice will immediately be sent to the **Ministry of Health** only if there is a connection between the death event and the use of the research product or the study process or if such a connection is highly probable, and the event is unanticipated (the message subject must state: "Death Incident").

### **5.3.3 Reporting an SAE other than death**

**5.3.3.1** There is no connection / there is a low probability of a connection to the research product or the study process. The Helsinki Committee Chairman will examine the report, and if he concludes that the SAE is unrelated, or that the probability is low that the SAE is related to the use of the research product or the study process (for example in cases of disease progression), he will document his decision using Form 13. The form will be sent **to the Investigator** and will include a decision to continue the trial.

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 35	Procedure Number 164/01

**5.3.3.2** There is a connection / a connection is highly probable / it is not possible to rule out a connection to the research product or the study process. If the Committee Chairman is of the opinion that there is a connection or that a connection is highly probable or that it is not possible to rule out a connection between the SAE and use of the research product or the study process, he will report his conclusion and the Investigator's opinion (the Sponsor's decision will only be sent if it is determined that the case is that of a USADE/ SUSAR) at the next meeting of the Helsinki Committee or to a limited panel defined in the Committee's work procedure. The Committee will decide whether to continue the trial / halt the recruitment of new subjects to the trial / discontinue the trial / other decision).

The discussion and the decision shall be documented using Form 14 (Part B) without an investigative team and brought to the attention of **the Investigator**. Notice will be immediately sent to the **Ministry of Health** only if there is a connection between the SAE and the use of the research product or the study process or if such a connection is highly probable, and the event is unanticipated (the message subject must state: "SUSAR").

**5.3.4 Additional reports received from Investigators:**

**5.3.4.1 RSI update** (IB or SmPC update) after approval in a recognized country. This document will be delivered to the Committee even before approval is received to conduct the trial.

**5.3.4.2 A Notice to the Medical Team** published by the Manufacturer or health authority in a recognized country, or new data published in the **professional medical literature** which has implications for the safety of the research product and use thereof in human subjects. This refers to information which includes

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 36	Procedure Number 164/01

any safety-related **prohibition, restriction or warning**. The information will be remitted to the Committee even before approval is received to conduct the trial.

**5.3.4.3 The conclusions of the Safety Committee** for the medical trial (DSMB / DMC) in which the decision was made to make modifications to the protocol which affect the safety of the patients or terminate the trial. This notice will be delivered to the Committee even before approval is received to conduct the trial.

**5.3.4.4 New findings** associated with the conduction of the trial or the development of the research product that are likely to affect the safety of the trial subjects. For example, a significant safety finding in animal trials which have recently been completed (such as: carcinogenicity); lack of efficacy of a research product used to treat a life threatening disease. This information shall be remitted to the Committee even before approval is received to conduct the trial.

**5.3.4.5** The decision in principle made by the **regulatory authority** of a recognized country, referring to the continuation of the trial due to safety concerns, including temporary or absolute termination thereof, as well as a decision to recommence the trial after its termination.

**5.3.4.6 Periodic line listing** – A concentrated list of the USADE / SUSAR events at a frequency of at least once every six months. The report will be accompanied by a **summary** of the main issues that arose regarding the safety of the research product within the time frame described in the report while **maintaining the blindness** of the study.

The Investigator shall attach a summary of the changes and findings regarding the safety issue and the implications thereof to the information to be remitted to the trial

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 37	Procedure Number 164/01

subjects (those who have been recruited or those who are to be recruited). In cases in which the consent form must be updated, the new data will also be attached to be remitted to the subjects, including time frames and the manner in which the subjects were contacted.

The Committee shall continue to handle the reports as detailed in Section 5.3.1 above. In cases in which information was filed before the approval to conduct the trial was granted (Form 7), the Committee shall reexamine the safety information and decide whether to continue to approve the trial. The Committee is not obligated to issue a revised Form 6 and Form 12 will suffice.

Notices to the **Ministry of Health** will only be sent in the event of a change in trial status to the 'Clinical Trials Protocols' email: [Protocols.clinicaltr@MOH.GOV.IL](mailto:Protocols.clinicaltr@MOH.GOV.IL). Each message will include the event details that lead to the change of status.

**TABLE 5:** Reports to the Ministry of Health

SAE Type	Connection to the research product	Time frame for reporting to the Institution Director	Time frame for reporting to the MOH	Terms for reporting to the MOH
<b>Death</b>	There is no connection / a low probability of a connection	-	-	-

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 38	Procedure Number 164/01

	There is a connection / a highly probable connection	Immediately	After discussion of the findings of the Investigative Committee	There is a connection to product / process and death is unexpected / unanticipated
<b>SAE other than death</b>	There is no connection / low probability of a connection	-	-	-
	There is a connection / a highly probable connection	Immediately	After the decision of the Committee or the Committee Chairman	There is a connection to product / process and death is unexpected / unanticipated
Additional safety reports	-	-	After the decision of the Committee or the Committee Chairman	Change in trial status

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 39	Procedure Number 164/01

**6. APPENDICES**

*Appendix 1 -*

*Description of the collection of the information, the classification and the reporting of adverse events*

		No	2	No	1
			Connected to Product?		Adverse Event Serious?
			yes		yes
DSUR	Continuous		Adverse		Serious
And	Safety		Reaction		Adverse
	Assessment		Its		Event
PSR			characteristics, frequency of appearance or severity are not in accordance with the RSI; consider reporting as unexpected		SAE

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 40	Procedure Number 164/01

	<b>Serious Adverse Reaction</b>	No Related to product? Yes
yes	3 Anticipated (appears in the RSI)? No <b>SUSAR / USADE</b>	
	Report to the Investigator	Report to the Ministry of Health
	Report to the Institutional Committee	

**RSI** – Reference Safety Information; **DSUR** – Development Safety Update Report;  
**PSR** – Periodic Safety Report;

**Questions 1 and 2.** Assessments that are performed by the Principle Investigator and the Sponsor. **Question 3.** In most cases, the assessment is performed by the Sponsor

*Appendix 2 – Form 13 and Form 14*

**Form 13 (A Sponsor Report Form with the required details may also be accepted)**

Date:

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 41	Procedure Number 164/01

Attention

The Chairman of the Institutional Helsinki Committee

Re: Notice of an SAE Suffered by a Subject in a Clinical Trial

**Trial Details**

Institutional Committee Application Number:		Ministry of Health Application Number:	
Trial topic (in Hebrew):			
Principle Investigator:		Department:	
Trial Protocol – Name or Number:		Version:	
The name of the Sponsor or the Sponsor representative in Israel:			
Contact person name:	Telephone No.	Fax No.	Email:

**Subject Details**

The initials of the subject's name: (at times does not appear in reports from overseas)	Subject code:	Age:	Sex: M / F
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**Event type :**

- Death
- Life threatening
- Leads to hospitalization or prolongation of current hospitalization (for example, due to the need for medical intervention, or due a risk of disability or due to it being life threatening)
- Causes disability or severe or prolonged incapacity
- Causes fetal death or distress or congenital defect

**Print Date June 14, 2018**



Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 43	Procedure Number 164/01

**FORM 14****Part A**

Date:

Attention

The Director of the Medical Institution

Re: Death of a Subject in a Clinical Trial – Investigative Team Report

Reference: Investigator's report pertaining to the death of a subject in a clinical trial

(Form 13) attached hereto

**Trial Details**

Institutional Committee Application Number:	Ministry of Health Application Number:
Principle Investigator:	Department:

**Investigation results** (Assess whether the inclusion and treatment were conducted in accordance with the study protocol; whether death is defined as an SAE in the protocol; whether this was a mishap; the extent of the connection between the event and the use of the research product or the study process etc.):

**The recommendations of the Investigative Team:**

(To terminate the study / to halt recruitment/ to modify the protocol / to amend the consent form / to continue the trial with no changes / other – specify)

\_\_\_\_\_  
The name of the

Investigative Team member

\_\_\_\_\_  
Signature\_\_\_\_\_  
Date

cc: The Chairman of the Institutional Helsinki Committee

\_\_\_\_\_  
**Print Date June 14, 2018**

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 44	Procedure Number 164/01

**Part B** – (Mark the type of event)

- 1) Summary of the conclusions of the Investigative Committee established to investigate the death incident.
- 2) A summary of the report of an SAE other than death for which there is a connection / a highly probable connection / a connection cannot be ruled out with the research product or the study process.

Date:

Attention

The Director of the Medical Institute

Re: Chairman / Helsinki Committee Decision**Discussion**

The expert opinion of the Principle Investigator (when a USADE/ SUSAR has been defined, the report from the Sponsor will also be added) and the recommendations of the Investigative Team (in the event of death).

Based on the information remitted to the Committee, our position is that

- 1) There is no connection / there is a low probability of a connection / a connection cannot be ruled out / it is highly probable that there is a connection / there is a connection between the event and the use of the research product or the study process.
- 2) The event was expected / unexpected / unanticipated.

**The decision has been made****Print Date June 14, 2018**

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 45	Procedure Number 164/01

(To terminate the study / to halt recruitment / to modify the protocol / to amend the consent form / to continue with trial with no changes / other – specify)

\_\_\_\_\_  
The Chairman of the Helsinki Committee

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

cc: The Principle Investigator

The Ministry of Health (only when a connection cannot be ruled out / it is highly probable that there is a connection / there is a connection and the event was unexpected / unanticipated).

Procedure for Reporting And Follow Up Of Reference Safety Information During The Course Of Human Clinical Trials	The Pharmacy and Enforcement Division
Page 46 of 46	Procedure Number 164/01

**7. AMENDMENTS**

<u>Version</u>	<u>Date</u>	<u>The amendment</u>
01		Version 01