修訂紀錄

版本	修訂日期	公告日期	執行日期	修訂原因
11.1	2018/10/26	2018/11/1	2018/12/1	依 AAHRPP 評鑑意見修訂

1.目的 Purpose

為提供所有經人委會核准的人體試驗，在試驗執行及追蹤期間，發生不良事件（Adverse Event, AE）、嚴重不良事件（Serious Adverse Event, SAE）與未預期事件(Unanticipated Problems, UP) 時之監測及通報依據。試驗過程中有時發生非預期性之風險,可能影響到風險/效益比率之相關資訊應該正確地通報，以確保受試者之權益。計畫主持人或試驗委託者必須在事件發生後依規定時限通報至人委會， 未預期事件亦需於追蹤審查報告（含期中及期末報告）內說明。

To provide the monitoring and report foundation to all IRB-approved human studies during study implementation and follow-up if there are any Adverse Event (AE), Serious Adverse Event (SAE) and Unanticipated Problems (UP). The unexpected risks occur during study period may affect the risk/benefit ratio, which shall be reported properly to ensure the rights of the subjects. The PI or Sponsor must report such event to the IRB within limited time frame. The Ups shall also be described in the follow-up review report (including the interim report and final report).

2. 適用範圍 Scope

本標準作業程序適用於所有本院核准之人體試驗，包含由計畫主持人(PI)、資料與安全監測委員會(Data & Safety Monitor Board，DSMB)、試驗委託者(Sponsor)、實地安全監測者(Monitor)、委員會委員(Members)或其他相關團

體(如 CRO 等)所提報之不良事件 (含嚴重不良反應)。臨床試驗之嚴重不良事件歸納為三大類：(1)本院之嚴重不良事件 (2)他院(國內、國外)之嚴重不良事件 (3)國外定期安全性報告。

This SOP is applicable to all KMUH-approved human studies, including the AE (including SAE) reported by the PI, Data & Safety Monitor Board (DSMB), sponsor, monitor, committee members or other relevant groups (e.g. CRO, etc.) The SAEs of clinical studies can be divided into three types: (1) SAE in KMUH; (2) SAE in other hospital (national and international); (3) International regular safety report.

3.參考文件 References

3.1 人體研究法 (2011年12月)

Human Subjects Research Act (December 2011)

3.2 人體試驗管理辦法(2009年12月)

Regulations on Human Trials (December 2009)

3.3 醫療器材優良臨床試驗作業規範 (2015年10月)

Regulations for Good Clinical Practice – Medical Devices (October 2015)

3.4 藥品優良臨床試驗準則（2014年10月）

Guidelines of Good Clinical Practice (October 2014)

3.5 International Conference on Harmonization, Guidance on Good Clinical Practice (ICH GCP) January 1996

3.6 嚴重藥物不良反應通報辦法(2004年8月)

Regulations for Reporting Severe Drug Adverse Reactions (August 2004)

3.7 OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events. Office for Human Research Protections (OHRP) Department of Health and Human

Services (HHS)，2007

3.8 DHHS: 45 CFR 46

4.名詞定義 Terminology

4.1 人體試驗：醫療機構依醫學理論於人體施行新醫療技術、新藥品、新醫療器材及學名藥生體可用率、生體相等性之試驗研究。

Human study: refers to the studies that medical institutes implement new medical technology, new drugs, new medical devices and generic drug bioavailability, bioequivalence based on medical theories.

4.2 不良事件(Adverse event, AE)：受試者參加試驗後所發生之任何不良情況。此項不良情況與試驗藥品/醫材間不一定具有因果關係。

Adverse Event (AE): refers to any adverse situations occur after the subject participating in the study. The adverse situation does not necessarily have cause-effect relationships with investigational drugs/medical devices.

4.3 藥品不良反應(Adverse drug reaction, ADR)：

Adverse Drug Reaction (ADR)

4.3.1 新藥品/醫材或新的使用途徑在臨床試驗中，特別是治療劑量過去未產生毒性及非預期之反應時，此項反應與試驗藥品間，應具有合理之因果關係，且此因果關係無法被排除。

For new drugs/medical devices or new administration routes in clinical studies, especially when the treatment dose did not create toxicity and UP reactions, there should be rational cause-effect relationships between the reaction and the investigational drug. The cause-effect relationships cannot be rule out, either.

4.3.2 關於已上市藥品，主要為此藥品產生毒性及非預期之反應，此反應係發生於一般常使用於人體以預防、診斷或治療疾病或調整生理功能之劑量。

For listed drugs, ADR often refers to the drug toxicity and UP reactions mainly generated by the drug. The reaction often occurs at the dose commonly used for human body to prevent, diagnose or treat diseases or modify physiological functions.

4.4 嚴重不良事件(Serious Adverse Event，SAE)：因試驗致發生包括

Serious Adverse Event (SAE) are caused by studies, including:

4.4.1 死亡：如病人死亡被認為係不良事件之直接結果。

Death: if patient's death is considered as the direct results of AE.

4.4.2 危及生命：如病人於發生不良事件時有死亡危險，或如繼續使用試驗產品可能造成病人死亡。例如:心臟節律器功能喪失、胃腸道出血、骨髓功能抑制、 輸液幫浦功能異常造成藥物劑量過量

Life-threatening: patients have risk of death during the occurrence of AE, or continue using investigational products may cause the death of patients. For example, dysfunction of pacemaker, GI bleeding, bone marrow functional inhibition, infusion pump dysfunction and cause drug overdose.

4.4.3 造成永久性殘疾：如不良事件對病人身體功能/結構、身體活動或生命品質,造成嚴重性、永久性的改變、損害或傷害。例如:因藥物引起過度凝集之腦血管意外、中毒、周邊神經病變。

Cause permanent disabilities: AE results in severe, permanent changes, damages or harm to patient's physical functions/structures, physical

activities or quality of life. For example, cerebrovascular accidents, poisoning, peripheral neuropathy caused by drug-induced over-agglutination.

4.4.4 胎嬰兒先天性畸型：如於懷孕前或懷孕期間暴露於藥品導致胎嬰兒不良結果。例如:母親懷孕時服用 diethylstilbestrol 造成女性罹患子宮頸癌、thalidomide 造成胎兒畸形。

Fetus congenital deformity: exposure to drugs and results in AE before or during pregnancy. For example, taking diethylstilbestrol during pregnancy may lead to female fetus cervical cancer and thalidomide leads to fetus deformity.

4.4.5 導致病人住院或延長病人住院期間：如因不良事件發生導致病人需住院或延長住院時間。例如：過敏性反應;偽膜性結腸炎、出血導致住院或延長住院時間。

Lead to hospitalization or prolonged hospitalization: AE leads to hospitalization or prolonged hospitalization. For example, allergic reactions, pseudomembraneous colitis, bleeding-induced hospitalization or prolonged hospitalization.

4.4.6 其他可能導致永久性傷害之併發症等嚴重不良反應者：懷疑因使用藥品造成 需要內科或外科介入治療以防止病人永久性失能或傷害。例如：Acetaminophen 劑量過量導致肝毒性，需以 acetylcysteine 治療以避免永久傷害;放射線設備造成之灼傷，需以藥物治療;螺絲破損需更換以避免長骨骨折之接合不良。

Other SAE that may lead to complications such as permanent damages: suspect drug use leading to the need of internal medicine intervention

or surgical intervention to prevent patients from permanent disability or damages. For example, Acetaminophen overdose-induced liver toxicity and thus requires acetylcysteine treatment to prevent form permanent damages; radiation-induced burning and thus requires medication treatment; screw wearing and thus requires replacement to prevent long bone fracture from malunion.

4.5 預期藥物不良反應(Expected ADR)：指根據計畫書/主持人手冊/藥品仿單/受試者同意書等資料上，有紀錄之藥物不良反應。

Expected ADR: refers to the drug ADR record on the protocol/investigator brochure/drug monograph/subject ICF.

4.6 非預期藥物不良反應(Unexpected ADR)：指計畫書/主持人手冊/藥品仿單/受試者同意書資料上，無記錄之藥物不良反應，屬非預期發生。

Unexpected ADR: refers to no drug ADR is found on the protocol/investigator brochure/drug monograph/subject ICF, which thereby belongs to expected event.

4.7 非預期嚴重藥品不良反應(Suspected unexpected serious adverse reaction, SUSAR)：為一種藥物使用後發生之不良且非預期之反應，此反應未曾於藥品訊息上記載（如：藥品臨床試驗主持人手冊；或上市藥品特性摘要不一致等)，或是可預期嚴重藥品不良反應「發生頻率」或「嚴重程度」超過預期。判定未預期嚴重不良反應(SUSAR)的三大要素：

Suspected unexpected serious adverse reaction (SUSAR): refers to an adverse and unexpected reaction after using a drug, which hasn't been noted on any drug information (e.g. investigator brochure of a pharmaceutical clinical trial, or inconsistent summary of listed drug properties); or serious expected drug

ADR, but the "frequency of incident" or "severity" has beyond the expectation. The three major elements to determine SUSAR are as follows:

4.7.1 因果相關性(Causality)：基於證據、或是可能的因果關係(Reasonable Possibility)，而判定在任何劑量下，對藥品所產生之有害的、非蓄意的個別反應，即稱之為不良反應(Adverse reaction)。若無證據懷疑因果關係，只能判定為不良事件(Adverse event, AE)。

Causality: any individual reactions to any doses but determined unharmful and unintentional based on evidence or reasonable possibility are called adverse reactions. If not evidence to prove the suspicion of causality, it can only be determined as adverse event (AE).

4.7.2 嚴重性(Seriousness)：係指死亡、危及生命、造成永久性殘疾、胎嬰兒先天性畸形、導致病人住院或延長病人住院時間、或其他可能導致永久性傷害需做處置等情形者，視為嚴重良反應。

Seriousness: serious reaction refers to the situations require corresponding handling such as death, life-threatening, permanent disability, fetus congenital deformity, hospitalization or prolonged hospitalization, or others that may lead to permanent damages.

4.7.3 非預期性(Unexpected)：係指未曾於藥品資訊文件上記載，或雖有記載但此不良反應的本質或嚴重程度有所改變。注意：若其它同類藥有此 ADR 證據而該品並無記載其中，仍需視為非預期。

Unexpected: refers to the events that haven't been noted on any drug information, or have been documented but the nature and severity of the ADR has been changed. Note: If other drugs in the same class have

such ADR evidence without any documentation, the reaction still shall be considered as unexpected.

4.8 CIOMS form：由Council for International Organizations of Medical Sciences組織訂定國際間通報SAE之標準通用格式。

CIOMS form: the standard generalized format created by the Council for International Organizations of Medical Sciences for reporting SAE internationally.

4.9 查驗登記新藥(IND)：具有治療功用製劑，於人體進行科學性研究，驗證其療效與安全性，並取得上市核准。

IND: preparations with therapeutic effects are used for human scientific research to verify the efficacy and safety and obtain the approval for listing.

4.10 非預期事件(Unanticipated Problem，UP)符合以下3個條件：

Unanticipated Problem (UP) shall meet the following three criteria:

4.10.1 非預期(Unexpected) :未記載於計畫書/受試者同意書/主持人手冊(Investigator Brochure)/藥品仿單(Product Monograph)之不良反應的事件或發生率嚴重性超過預期之情形則稱為未預期

Unexpected: the severity or incidence of AE not stated in the protocol/subject ICF/investigator brochure/product monograph have exceeded expected situations is called unexpected.

4.10.2 可能相關(Possible)

4.10.3 對受試者及其他研究人員之傷害（身體、心理、經濟及社會層次）超過已知的風險

The damages to subjects or other research personnel (physical,

psychological, economic and social levels) may have exceed known risks.

5.作業內容 Scope of operation

5.1流程 Process

程序 Procedure	權責 Rights and responsibilities	相關文件 Related documents
院內嚴重不良事件及非預期問題通報 The report of in-hospital AE and UP	計畫主持人與計畫相關人員 Principal Investigator and protocol-related personnel	院內嚴重不良事件及非預期問題通報表 The report of in-hospital AE and UP *衛福部藥物不良反應通報表 MOHW Drug ADR Report Form *臨床試驗嚴重不良事件通報回函 Reply to clinical trial SAE report *嚴重不良事件及非預期問題通報摘要表 SAE and UP report summary form *其他嚴重不良事件相關文件 Other SAE-related documents
受理 Receive	行政人員 Administrative staff	院內嚴重不良事件及非預期問題送審事宜 Matters regarding submitting in-hospital SAE and UP 1.試驗計畫之預期副作用資料 The expected side effects of the study 2.嚴重不良事件及非預期問題審查意見表 SAE and UP review comment form
審查 Review	執行秘書/審查專家 Executive secretary/Review experts	嚴重不良事件及非預期問題審查意見表 SAE and UP review comment form

決議 Resolution	委員會 Board	嚴重不良事件及非預期問題彙整資料及決議 Summary and resolutions of SAEs and UP
核定 Approved	主任委員 Committee director	會議紀錄 Meeting minutes
通知/存查 Notification/Retain for reference	行政人員 Administrative staff	1. 會議紀錄 Meeting minutes 2.決議通知表 Resolution notification form

5.2 職責Responsibilities

5.2.1 計畫主持人: 通報 SAE 或 UP

Principal Investigator: shall report the SAE or UP.

5.2.2 執行秘書/審查專家：進行風險與利益評估，針對超過微小風險極可能影響受試者安全之事件提交於審查會議審查。

Executive secretary/Review experts: shall conduct risk/benefit assessments, and submit the events with greater increase minimal risks that may affect the safety of the subjects to the IRB meeting for review.

5.2.3 行政人員：行政審查通報文件之完整性。將審查委員會核定結果彙整通知計畫主持人。

Administrative staff: shall keep the completeness of the administrative review reports and summarize and inform the PI about the review results.

5.2.4 主任委員：核定嚴重不良事件審查結果，必要時裁示是否召開臨時會議。

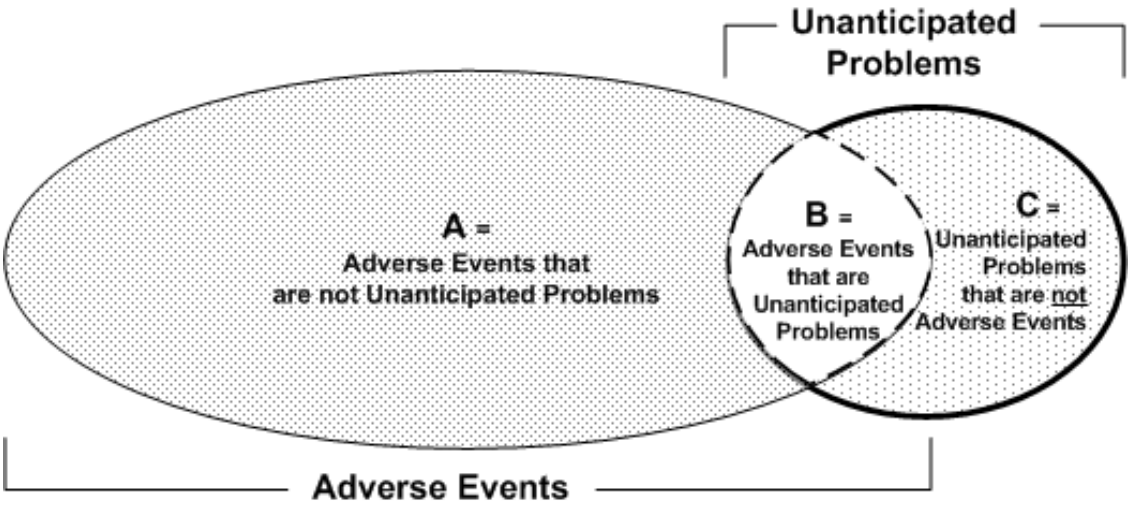
Committee director: shall review and approve the review results of the

SAE and decide whether it is required to convene temporary meeting if necessary.

5.3細則Rules

5.3.1 計畫主持人判斷是否符合通報範圍：根據美國 OHRP 關於 UP 之通報及審查指引，以下圖 B (AE 且為 UP)及 C (UP 但非 AE)範圍之事件，需以 UP 通報 IRB，A 範圍為 AE 但非 UP，不用以 UP 通報 IRB。

The PI will determine whether it is within the scope of report.



Under 45 CFR part 46: Do not report A, Do report (B+C)

5.3.2 院內事件通報方式：計畫主持人經由 PTMS 系統進行通報，未於 PTMS 系統登錄之案件，繳交電子檔。

In-hospital report: the PI shall report through the PTMS system. For those haven't been registered in the PTMS system, the PI shall submit electronic files.

5.3.3 通報時效性（SAE、UP）

The time frame for reporting

5.3.3.1 死亡或危及生命案件獲知日 7 日曆天內通報，並於 15 日曆天內提供詳細書面資料

For death or life-threatening cases, the PI shall report such case within 7 days after receiving the information, and provide detailed written reports with 15 days.

5.3.3.2 死亡或危及生命以外案件獲知日起 15 日曆天內通報,並提供詳細書面資料

For cases other than death or life-threatening, the PI shall report such case within 15 days after receiving such information and provide detailed written reports.

5.3.4 審查 Review

5.3.4.1 送交審查的文件包括：

The documents submitted for review include as follows:

A.檢附最新核准版本之主持人手冊、計畫書、受試者同意書。

The most recent approved version of investigator brochure, protocol and subject ICF.

B.計畫主持人填寫之嚴重不良事件及非預期問題通報表（附件三）

The PI shall fill in the SAE and UP Report Form (Attachment 3).

C.事件發生前後說明

The descriptions before and after the event.

D.其他計畫主持人認定需要提交之必要文件

Other documents that the PI believes required for submission.

5.3.4.2 行政人員確認文件齊備後，於 2 工作日內將所有通報文件資料送交執行秘書/審查專家，執行秘書/審查專家於 5 工作日內完成填

寫審查意見於嚴重不良事件及非預期問題審查表(附件四)。使用 PTMS 線上系統進行審查者，則以線上系統之審查介面審查。審查結果得為「存查」、「提審查會議討論」。

After the administrative staff have confirmed that all documents are prepared completely, they will send all report files to the executive secretary/review experts within 2 working days. The executive secretary/review expert shall complete the review comments on the SAE and UP Review Form (Attachment 4) within 5 working days. For those who use PTMS online system for review, please use the online interface to conduct report review. The review results could be “retain for reference” or “report to the review meeting for further discussion”.

5.3.4.3 若執行秘書/審查專家建議主任委員召開緊急會議討論時，則依據 SOP 召開緊急會議。

If the executive secretary/review expert has recommended the committee director to convene an emergency meeting, he/she shall convene the meeting in accordance with the SOP.

5.3.5 決議/存查 Resolutions/Retain for reference

5.3.5.1 本院發生之嚴重不良事件及事故，經審查專家判定為 UP、SUSAR 或可能具有因果關係(Naranjo score≧5)者，列入審查委員會討論並決議，其他嚴重不良事件予以備查。

The SAE and incidents occurred in KMUH which has been determined by the review experts as UP,SUSAR or with causality possibility (Naranjo score≧5), will be scheduled into Board Meeting

for discussion and making resolutions. Other SAEs will also be retained for reference.

5.3.5.2 經委員充分討論後,委員會得依據多數人意見採行下列多項處置:

After fully discussion between the members, the IRB may take the following actions based on most people's comments:

A.要求主持人提供進一步資訊。

Ask the PI to provide further information.

B.暫停試驗。

Suspend the study.

C.終止試驗。

Terminate the study.

D.當有可能影響受試者繼續參與研究意願的資訊時，需通知已加入研究的受試者。

If any information that may affect the subject's willingness to continue participate in the study is uncovered, the subjects that have participated in the study shall also be informed.

E.提供曾參與研究的受試者額外的資訊。

Provide additional information about the subjects who had participated in the study.

F.修訂計畫書並入會審查。

Amend the protocol and report to the IRB for review.

G.修訂受試者同意書並入會審查，且須重新取得正在參與試驗的受試者同意。

Amend subject ICF and report to the IRB for review. The consents

from subjects who are currently participating in the study shall be re-obtained.

H.監測知情同意過程。

Monitor the process of informed consent.

I. 監測研究。

Monitor the study.

J. 修改持續審查的頻率。

Amend the frequency of continuing review.

K.轉介到其他機構。

Refer to other institutes.

L. 同意核備。

Approve for reference.

M.其他可能需要的受試者保護措施。

Other subject protection measures that may be required.

5.3.6 若人委會決議存查，應記錄試驗准予繼續執行。

If the IRB decides to retain for reference, the record shall be “the continuance of the study implementation is approved”.

5.3.7 行政人員於會議後 10 工作日內正式以書面通知計畫主持人、臨床研究受試者保護中心及機構主管會議決議，並請依會議決議執行。

The administrative staff shall inform the PI, CHSP and superintendent of KMUH about the meeting resolution in writing within 10 working days after the meeting, and ask the PI to implement the study based on the resolutions.

5.4 院外發生之嚴重不良事件：試驗委託者依據嚴重不良事件通報原則填寫多

中心臨床試驗安全性通報表，並向人委會及計畫主持人通報。行政人員將登錄於資料庫備查。

SAE occurs in other hospital: the Sponsor shall fill in the multicenter clinical trial safety report form based on the principles of reporting SAEs, and report the SAEs to the IRB and the PI. The administrative staff will upload such information in the database for reference.

5.5 行政人員每月將嚴重不良事件、SUSAR及UP審查結果彙整至各審查會決議。並每季彙整相關資料及審查會決議依要求送至醫品室備查。

The administrative staff will summarize the review results of SAEs、SUSARs and UP monthly and report to individual review meeting for making resolutions. The administrative staff will also summarize related information and review resolutions to the Medical Quality Control Office for reference, CSHP according to the requirement .

5.6 行政人員將相關文件歸檔，所有文件須保存至該臨床試驗案結案後至少二年。

The administrative staff shall archive all relevant files. All files shall be retained for at least 2 years after the clinical trial has closed.

6.附件 Attachment

6.1 附件一.1 (KMUH/IRB/AF/3.3-01.1/11.0) 嚴重不良事件通報原則

Attachment 1.1 (KMUH/IRB/AF/3.3-01.1/11.0) Principles to Report SAEs

附件一.2 (KMUH/IRB/AF/3.3-01.2/11.0) 非預期事件通報原則

Attachment 1.2 (KMUH/IRB/AF/3.3-01.2/11.0) Principles to Report UP

6.2 附件二(KMUH/IRB/AF/3.3-02/11.0) 臨床試驗嚴重不良事件通報回函

Attachment 2 (KMUH/IRB/AF/3.3-02/11.0) Reply to Clinical Trial SAE

Report

6.3 附件三(KMUH/IRB/AF/3.3-03/11.0) 嚴重不良事件及非預期問題通報表

Attachment 3 (KMUH/IRB/AF/3.3-03/11.0) SAE and UP Report Form

6.4 附件四(KMUH/IRB/AF/3.3-04/11.0) 嚴重不良事件及非預期問題審查意見表表

Attachment 4 (KMUH/IRB/AF/3.3-04/11.0) SAE and UP Review Comment Form

6.5 附件五(KMUH/IRB/AF/3.3-05/11.0) 臨床試驗計畫嚴重不良事件審查決議通知

Attachment 5 (KMUH/IRB/AF/3.3-05/11.0) Clinical Trial SAE Review Resolution Notification