DATE	March 24, 2011
日期:	**2011 年 3 月 24 日**
TO:	Protocol HPTN 058 Principal Investigators, Study Coordinators and Study Staff
送：	HPTN058 方案主要研究者、研究协调员和研究工作人员
FROM:	HPTN 058 Protocol Team:
从：	HPTN058 方案小组
SUBJECT:	Letter of Amendment #2 to Protocol HPTN 058, Version 2.0 dated 16 September 2008 (IND # 73,797), entitled ***A Phase III randomized controlled trial to evaluate the efficacy of drug treatment in prevention of HIV infection and death among opiate dependent injectors***
主题：	**《评价药物治疗对注射阿片类制剂人群预防 HIV 感染和死亡效果的III期随机对照临床试验》**2008 年 9 月 16 日 2.0 版本(IND # 73,797)的第 2 号修订信

The following information impacts the HPTN 058 study and must be forwarded to your institutional review board (IRB)/ethics committee (EC) as soon as possible for their information and review. This must be approved by your IRB/EC before implementation.

以下信息影响 HPTN058 研究，必须尽快将信息递交你处伦理审查委员会（IRB/EC）审查。在执行前必须获得你处 IRB/EC 批准。

The following information may also impact the sample informed consent. Your IRB/EC will be responsible for determining the process of informing subjects of the contents of this letter of amendment (LOA).

以下信息也可能影响知情同意。你处伦理审查委员会负责决定将修订信（LOA）内容通知参加者的进程。

Upon receiving final IRB/EC and any other applicable regulatory entity (RE) approval(s) for this LOA, sites are required to submit an LOA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LOA once the DAIDS PRO verifies that all the required LOA registration documents have been received and are complete. Sites will not be able to implement this LOA until they have received an LOA registration notification from the DAIDS PRO. A copy of the DAIDS PRO LOA registration notification along with this letter and any IRB/EC correspondence should be retained in the site's regulatory files.

收到伦理审查委员会和相关法规机构（RE）对本修订信的批准后，现场立即向在法规支持中心（RSC）的艾滋病署方案注册办公室（DAIDS PRO）提交一份修订信注册信息包。一旦 DAIDS 方案注册办公室核实已收到且完成了所有要求的修订信注册文件，现场将收到一份注册通知。在收到 DAIDS 方案注册办公室的修订信注册通知前，现场不能执

行本修订信。随信的 DAIDS 方案注册办公室修订信注册通知副本、修订信及任何伦理委员会的信件应被保存在现场规章文件夹中。

The purpose of this LOA is to incorporate use of Version 2.0 of the Manual for Expedited Reporting of Adverse Events to DAIDS (DAIDS EAE Manual). The following language will replace the Expedited Adverse Event Reporting section of the HPTN 058 Protocol Version 2.0 dated 16 September, 2008.

本修订信的目的是为了配合 2.0 版不利事件快速上报至 DAIDS 报告手册（DAIDS EAE 手册）的使用。以下文字将替代 2008 年 9 月 16 日 2.0 版 HPTN058 方案中的快速上报的不利事件报告部分。

Additions are noted in **bold**. Deletions are noted via ~~**strikethrough.**~~

增加的内容用**粗体**标注，删除的内容加□□□标注。

I. Protocol Section 6.2 has been revised as follows:方案 6.2 部分做如下修订：

~~**6.2 Adverse Event Reporting Requirements**~~

~~An adverse event (AE) is defined as any untoward medical occurrence in a clinical research participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product.~~

~~A serious adverse event (SAE) is any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect (April 1996 International Conference on Harmonisation (ICH), Good Clinical Practice: Consolidated Guidance, (ICH E6). Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above may also be considered to be serious (October 1994 ICH guidance (E2A), Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). For the purposes of this study, outpatient or inpatient hospital/medical facility admission for drug addiction treatment or rehabilitation will not be considered a SAE.~~

~~The expedited adverse event (EAE) reporting requirements and definitions for this study and the methods for expedited reporting of adverse events (AEs) to the DAIDS Regulatory Compliance Center (RCC) Safety Office are defined in "The Manual for Expedited Reporting of Adverse Events to DAIDS" (DAIDS EAE Manual), dated 6 May~~

2004. AEs that meet the criteria for expedited reporting to DAIDS must be reported on the DAIDS Expedited Adverse Event Reporting Form (EAE Reporting Form) and sent within 3 business days of site awareness to the DAIDS Safety Office. Both the DAIDS EAE Manual and the EAE Reporting Form are available on the RCC website: http://rcc.tech-res-intl.com and will be included in the Study Specific Procedures Manual. Contact and submission information for the DAIDS Safety Office is included in the EAE Manual, on the front page of the EAE Reporting Form (which is designed to serve as the cover page for submissions) and in the SSP Manual.

Specifically, the 'standard' level of reporting defined in the DAIDS EAE manual will be followed for the first 52 weeks of follow-up for participants in both study arms (from study enrollment until the participant completes 52 weeks of follow-up or is terminated from study participation for any reason). Conditions and illnesses identified in participants prior to randomization will be considered pre-existing conditions and will not be reported as adverse events, unless the condition worsens after randomization (increases in severity or frequency), in which case it would be reported as an AE.

The study drug in HPTN 058 is the BUP/NX combination (Suboxone), provided for 52 weeks to participants randomized to the substitution arm and, for participants randomized to the detoxification arm, up to 18 days beginning at randomization and/or within 30 days of the six month visit; therefore it is the relationship of all AEs to this product that is to be considered in determining the reporting requirements for each AE (e.g., whether the AE must be reported in an expedited manner to DAIDS).

All adverse events occurring in participants through week 52 will be graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, dated December 2004, which will be included in the SSP Manual and is available at the following website: http://rcc.tech-res-intl.com. All serious adverse events (SAEs), regardless of severity or relatedness, and all AEs that otherwise meet the criteria for expedited reporting to DAIDS (EAEs) occurring to participants in either study arm through week 52 will be reported on a standard AE DataFax case report form for entry into the study database. AEs that are not serious or do not otherwise meet the criteria for expedited reporting to DAIDS will be recorded in the study source documentation but will not be included in the study database. As noted above, for the purposes of this study, outpatient or inpatient hospital/medical facility admission for drug addiction treatment or rehabilitation will not be considered a serious adverse event.

There will be no active reporting of adverse events after the period specified above (52 weeks of follow-up); however, unexpected, serious adverse drug reactions must be reported if the study site staff become aware of the events on a passive basis, i.e., from publicly available information.

Information on all AEs included in the study database will be included in annual reports to the US FDA, and other applicable government and regulatory authorities. The investigators will report information on AEs and SAEs to the responsible Institutional Review Boards/Ethics Committees in the US and the host countries in accordance with applicable regulations and individual IRB/EC requirements.

6.2 □□□□□□□□□

不利事件（AE）是指临床研究中研究对象使用研究产品时发生的不幸医学事件，该事件与研究产品没有必然的因果关系。如上所述，不利事件可能是某些不适的、意外的症状（如：异常的实验室结果等）、与暂时应用研究产品相关的体征或疾病，不管体征和疾病否由该研究产品所致。

严重不利事件（SAE）包括以下任何一种不幸医疗事件：任何剂量引起的死亡、危及生命、需要住院治疗或延长住院治疗、造成严重的永久残疾或失能、引起先天异常或出生缺陷（(April 1996 International Conference on Harmonisation (ICH), Good Clinical Practice: Consolidated Guidance, (ICH E6)），虽不会立即危及生命、导致参加者死亡或需要住院治疗，但却给病人带来危害并需要采取干预措施预防上述情况发生的医疗事件也应归为严重的不利事件(October 1994 ICH guidance (E2A), Clinical Safety Data Management: Definitions and Standards for Expedited Reporting)。对本研究来说，门诊或、住院或使用医疗设施戒毒治疗或康复治疗不属于 SAE。

发生不利事件应迅速报告，快速报告要求和有关定义及如何向 DAIDS 规章依从性中心 (RCC) 安全性办公室报告请参见“不利事件快速上报至 DAIDS 报告手册（DAIDS EAE 手册）--2004 年 5 月 6 日版”。对于满足 DAIDS 快速报告条件的不利事件必须填写不利事件快速报告表（EAE 报告表），然后在现场知道副反应发生的 3 个工作日内将表提交给 DAIDS 安全办公室。DAIDS EAE 手册及报告表可以从 RCC 网站下载，网址为：http://rcc.tech-res-intl.com，本研究的特定程序手册 SSP 包含上述内容。在 EAE 报告表首页和 EAE 手册中也有 DAIDS 安全办公室的联络方式和资料发送方式。

需要特别指出的是：两组研究对象前 52 周（从研究对象入选到完成 52 周的随访，或因任何原因终止研究）的随访应该遵守 DAIDS EAE 手册所定义的“标准水平”。随机分组前发现的临床症状或疾病都应视为参加者既往健康状况不作不利事件报告，除非于随机分组后恶化(程度加重或发作频率增加)，则按不利事件报告。

HPTN058 项目研究药物为丁丙诺啡/纳诺酮混合制剂（又称为 BUP/NX），替代治疗组将服用该药物 52 周，而戒毒组则在随机化分组后的 18 天内和/或第 6 个

~~月随访的 30 天内服用；因此报告不利事件前必须了解它与研究产品之间的关系（如：不利事件是否应该快速报告给 DAIDS）。~~

~~分组后的 52 周内研究对象发生的任何不利事件都应根据 DAIDS "成人和儿童不利事件严重程度分级表（Table for Grading the Severity of Adult and Pediatric Adverse Events，2004 年 12 月版）"进行分级，SSP 手册有该分级表内容或者从 http://rcc.tech-res-intl.com 网址上下载。52 周的研究期内任一组研究对象发生的严重不利事件（无论严重程度或有无关联）和所有其他满足 DAIDS 快速报告标准的副反应，都应以标准的 AE 病例表形式报告以录入研究数据库。根据美国 DAIDS 毒性分级表对 52 周内发生的所有 AE 进行分级。不严重或者不符合迅速报告标准的 AE 只在原始文件上进行记录而不进入到研究数据库。如前所述，就研究目的而言，门诊、住院或使用医疗设施解毒治疗或康复治疗不属于 SAE。~~

~~52 周随访期外发生的不利事件不需要主动上报，但研究人员一旦通过被动方式（如公共信息）得知有意外情况、严重的不利事件发生，必须报告。~~

~~数据库中所有的不利事件资料以年报形式提交给美国食品药品管理局（FDA）、相关政府机构和管理机构。项目负责人应根据有关法规和伦理审查委员会（IRBs/Ecs）的要求，向美国和现场伦理审查委员会报告研究过程中发生的 AE 和 SAE 信息。~~

6.2 Adverse Event (AE) and Expedited Adverse Event (EAE) Reporting 不利事件（AE）和快速上报的不利事件（EAE）报告

6.2.1 Adverse Event Reporting to DAIDS 向 DAIDS 报告的不利事件报告

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

不利事件（AEs）快速报告的要求、定义和方法见 2.0 版 DAIDS EAE 手册，该手册可从 RSC 网站 http://rsc.tech-res.com/safetyandpharmacovigilance/下载.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the

DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

向 DAIDS 快速报告不利事件 必须使用 DAIDS 不利事件报告系统（DAERS），这个基于网络的报告系统。遇系统故障或技术难题，快速上报的不利事件可能通过 DAIDS 不利事件快速报告表提交，有关 DAERS 的问题，请通过 DAIDS-ESSupport@niaid.nih.gov 联系 DAIDS-ES，也可以通过 DAERS 自身的应用程序发送现场疑问。

Where DAERS has not been implemented, sites will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

在未运行 DAERS 的地方，现场通过填写最新的 DAIDS EAE 表上的信息提交快速上报的不利事件。该表可从 RSC 网站 http://rsc.tech-res.com/safetyandpharmacovigilance/下载。有关 EAE 报告的疑问，请联系 RSC(DAIDSRSCSafetyOffice@tech-res.com)。

AEs that are not serious or do not otherwise meet the criteria for expedited reporting to DAIDS will be recorded in the study source documentation but will not be included in the study database. For the purposes of this study, outpatient or inpatient hospital/medical facility admission for drug addiction treatment or rehabilitation will not be considered a serious adverse event.

非严重的或者不符合快速上报至 DAIDS 的不利事件将记录在研究源文件中，但不进入研究数据库。对本研究来说，门诊、住院或使用医疗设施进行戒毒治疗或康复治疗不属于严重不良事件。

6.2.2 Reporting Requirements for this Study 本研究的报告要求

- **The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.**
- **本研究使用 2.0 版 DAIDS EAE 报告手册定义的严重不利事件报告类别。**
- **The study agents for which expedited reporting are required are BUP/NX (Suboxone®), provided for the first 52 weeks to participants.**
- **要求快速报告的研究产品是在□52 周提供给参加者的 BUP/NX (Suboxone ®)。**

6.2.3 Grading Severity of Events 事件的严重程度分级

The most current Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) is used and is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

使用最近的 DAIDS 成人和儿童不利事件严重程度分级表（DAIDS 不利事件分级表），可从 RSC 网站 http://rsc.tech-res.com/safetyandpharmacovigilance/下载。

6.2.4 Expedited AE Reporting Period 快速不利事件上报周期

- **The expedited AE reporting period for this study is from the time that the first dose taken of Suboxone® up until Week 52. For the purposes of this study, outpatient or inpatient hospital/medical facility admission for drug addiction treatment or rehabilitation will not be considered a serious adverse event.**
- **本研究的快速不利事件上报期间是从第一次服用 Suboxone®到第 52 周。对本研究来说，门诊、住院或使用医疗设施进行戒毒治疗或康复治疗不属于严重不良事件。**
- **After Week 52, all deaths will continue to be reported. After Week 52, the protocol defined AE reporting period is concluded and only SUSARs as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).**
- **52 周后，所有死亡事件继续报告。52 周后，方案定义的不利事件上报周期结束，如果研究人员被动获知该事件（从公开的信息），仅 2.0 版 EAE 手册定义的 SUSARs 报告给 DAIDS。**

Note: Information on all AEs included in the study database will be included in annual reports to the US FDA, and other applicable government and regulatory authorities. The investigators will report information on AEs and SAEs to the responsible Institutional Review Boards/Ethics Committees in the US and the host countries in accordance with applicable regulations and individual IRB/EC requirements.

注意：数据库中所有的不利事件资料以年报形式提交给美国食品药品管理局（ FDA）、相关政府机构和管理机构。项目负责人应根据有关法规和伦理审查委员会的要求，向美国和现场伦理审查委员会报告研究过程中发生的 AEs 和 SAEs 信息。

II. The original Appendix VI has been has been revised as follows: 原附录 VI 做如下修订：

APPENDIX VI: HPTN 058 Adverse Event Reporting and Documentation Requirements*
附录 VI: HPTN 058 不良事件报告及存档要求*

	Adverse Event	Relationship to Study Product	Record event and grade in primary source documents	AE Log (DataFax to SDMC)	EAE Form (to DAIDS RCC within 3 business days of site awareness)
Serious Adverse Events	Results in Death	Regardless of relationship	YES	YES	YES
	Results in persistent or significant disability or incapacity	Regardless of relationship	YES	YES	YES
	Is a congenital anomaly or birth defect or fetal loss	Regardless of relationship	YES	YES	YES
	Requires or prolongs hospitalization	Probably not related Possibly related Probably related Definitely related	YES	YES	YES (if meets one of the relationship criteria)
	Requires intervention to prevent significant incapacity/permanent disability or death	Probably not related Possibly related Probably related Definitely related	YES	YES	YES (if meets one of the relationship criteria)
	Is life-threatening (including all Grade 4 AEs)	Probably not related Possibly related Probably related Definitely related	YES	YES	YES (if meets one of the relationship criteria)
	All other SAEs	Not related to study product	YES	YES	NO (unless directly related to study participation)
Non-Serious Adverse Events	All non-serious AEs	Regardless of relationship	YES	NO	NO

* All AEs must be documented in the participant's source record, regardless of seriousness, severity or relatedness. AEs will only be documented and reported to the SDMC/DAIDS as appropriate for participants in both study arms through week 52 of follow-up.

	不良事件	与研究产品的关系	在源文件中记录事	AE 日志 (DataFax to	EAE 表 (在现场接到报告的 3 个

			件和分级	SDMC)	工作日内报告给DAIDS RCC)
严重不良事件	导致死亡	不考虑与研究产品的关系	是	是	是
	导致持续的或明显的残废或能力丧失	不考虑与研究产品的关系	是	是	是
	导致先天异常或出生缺陷或流产	不考虑与研究产品的关系	是	是	是
	需要住院治疗或延长住院时间	可能无关 可能相关 很可能相关 肯定有关	是	是	是(如果满足其中一个标准)
	需要干预以预防严重的能力丧失/残废或死亡	可能无关 可能相关 很可能相关 肯定有关	是	是	是(如果满足其中一个标准)
	威胁生命(包括所有第4级的不良事件)	可能无关 可能相关 很可能相关 肯定有关	是	是	是(如果满足其中一个标准)
	所有其他严重不良事件	*与研究产品无关*	是	是	*否(除非与直接参与研究有关)*
非严重不良事件	*所有非严重不良事件*	*不考虑与研究产品的关系*	是	是	否

*不考虑严重性、强度或关系，所有不良事件必须记录在参加者的原始文件记录中。仅在随访的前52周记录两组参加者不良事件，并根据情况报告给SDMC/DAIDS。

APPENDIX VI: HPTN 058 ADVERSE EVENT REPORTING AND DOCUMENTATION REQUIREMENTS

附录 VI：HPTN058 不利事件报告及存档要求

	ADVERSE EVENT	RELATIONSHIP TO STUDY PRODUCT	Record event and grade in primary source documents	EAE FORM (to DAIDS RSC within 3 business days of site awareness)
Serious Adverse Events	Results in Death	Regardless of relationship	YES	YES
	Is life-threatening[1]	Regardless of relationship	YES	YES
	Requires inpatient hospitalization or prolongation of existing hospitalization[2]	Regardless of relationship	YES	YES
	Results in persistent or significant disability or incapacity	Regardless of relationship	YES	YES
	Is a congenital anomaly/birth defect[3]	Regardless of relationship	YES	YES
	Is an important medical event (may jeopardize the patient or may require intervention to prevent one of the other outcomes above)[4]	Regardless of relationship	YES	YES
Non-Serious Adverse Events	All non-serious AEs	Regardless of relationship	YES	NO

	不利事件	与研究产品的关系	在源文件中记录事件和分级	EAE 表（在现场接到报告的 3 个工作日内报告给 DAIDS RSC ）
严重不利事件	导致死亡	不考虑与研究产品的关系	是	是
	威胁生命 [1]	不考虑与研究产品的关系	是	是
	需要住院治疗或延长住院	不考虑与研究产品	是	是

	时间 [2]	的关系		
	导致持续的或明显的残废或能力丧失	不考虑与研究产品的关系	是	是
	导致先天异常/出生缺陷 [3]	不考虑与研究产品的关系	是	是
	重要医疗事件（可能危害参加者或可能需要干预以防止上述其它情况之一发生）[4]	不考虑与研究产品的关系	是	是
非严重不良事件	*所有非严重不良事件*	不考虑与研究产品的关系	是	否

- **NOTE：All AEs must be documented in the participant's source record, regardless of seriousness, severity or relatedness. AEs will only be documented and reported to the SDMC/DAIDS as appropriate for participants in both study arms through Week 52 of follow-up. After week 52, SUSAR reporting is in effect (http://rsc.tech-res.com/safetyandpharmacovigilance/).**
- **注意：不考虑严重性、程度或相关性，所有不利事件必须记录在参加者的源文件记录中。仅记录两组参加者前52 周随访期间的不利事件，并根据情况报告给SDMC/DAIDS。52周后只报告SUSAR（http://rsc.tech-res.com/safetyandpharmacovigilance/）。**

1: "Life-threatening" refers to an event in which the patient was at risk of death at the time of the event. It does NOT refer to an event that hypothetically might have caused death if it were more severe.

1、"威胁生命"是指在事件中参加者有死亡的危险，不是指假设如果事件更严重，可能导致死亡。

2: Per ICH SAE definition, hospitalization is NOT an adverse event (AE), but is an outcome of the event. DO NOT REPORT: Any admission unrelated to an AE (e.g., for labor-delivery, cosmetic surgery, administrative or social admission for temporary placement for lack of a place to sleep); protocol-specified admission (e.g., for a procedure required by protocol); admission for diagnosis or therapy of a condition that existed before receipt of study agents(s) and has not increased in severity or frequency as judged by the clinical investigator. In addition inpatient hospital/medical facility admission for drug addiction treatment or rehabilitation will not be considered a serious adverse event. (NOTE: A new AIDS-defining event in a subject already known to be HIV-infected would be considered an increase in severity of a pre-existing condition [HIV infection] and would be reportable.)

2、根据 ICH SAE 定义，住院治疗不是不利事件（AE），但是事件的后果。不用报告：任何与不利事件无关的住院（例如：分娩、美容手术、因缺乏睡觉处所行政或社会临时安置入院）；方案规定的住院（例如：作为方案要求的一个程序）；在使用研究产品前已住院诊断或治疗，临床研究者判断严重程度和发作频率没有增加。此外，住院或使用医疗设施进行戒毒治疗或康复治疗不属于严重不良事件。（注意：在项目中，已经知道 HIV 感染出现新的 AIDS 相关事件将被认为是之前状态[HIV 感染]严重程度的增加，并被报告。）

3: Clinically insignificant physical findings at births including those regarded as normal variants do NOT meet reporting criteria. If a clinically significant anomaly is reported, all findings (including those of no individual

significance) should be included in the same report. For example, do NOT report an isolated finding of polydactyly (extra fingers or toes) or Mongolian spot in an infant. But if either finding occurred with a major cardiac defect, report all findings in the SAE report.

3、出生时临床无意义的查体发现，包括被认为是正常变异的情况，不作为上报标准。如果有意义的临床变异被报告，所有发现（包括无特殊意义的发现）应该包含在同一报告中。例如，不用上报一个单独的多指畸形（多手指或脚趾），或婴儿胎记。但是，任一发现与心脏缺陷同时发生，将在 SAE 报告中上报所有发现。

4: Examples are intensive treatment in the emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; etc.

4、例如，在急症室或家里针对过敏性支气管痉挛进行的特别治疗，不导致住院的血液异常或抽搐，等。

The above information will be incorporated into the next version of the protocol at a later time if it is amended.

如果方案被修订，上述信息随后将并入下版方案中。