DNDi
Drugs for Neglected Diseases *initiative*

REGISTERED

Mr Ludovic Barra
Financial officer
IRD-PHPT
187/10 Changklan Road, Changklan,
Muang
Chiang Mai 50100
Thailand

Geneva, February, 22nd 2013

RE: Technical Services Agreement

Dear Luc,

Please find enclosed :

☒ a fully executed copy of the aforementioned contract for your records.

☐ two partially executed copies of the aforementioned contract. Please arrange for all copies to be signed, dated and initialed. Thereafter retain one original for your records and return the other fully executed copy back to my attention at your earliest convenience.

Thank you for your assistance.

Best regards,

Christophine MARTY MOREAU
Procurement and Contract officer

15 Ch. Louis-Dunant · 1202 Geneva
Switzerland
Tel: +41 (22) 906 92 30 · Fax: +41 (22) 906 92 31
www.dndi.org

DNDi
Drugs for Neglected Diseases *initiative*

PHPT

Technical Services Agreement

made on February 1, 2013 ("the Effective Date")

Parties: **Drugs for Neglected Diseases Initiative**, a Swiss foundation having its principal office at 15 ch. Louis-Dunant, 1202 Geneva, Switzerland ("**DNDi**")

and

AMS-PHPT, a Collaborative Medical Science Research Unit by the Faculty of Associated Medical Sciences of Chiang Mai University, a Public University of Thailand, having its principal office at 110 Intawaroros Rd. T. Sripoom, Muang, Chiang Mai 50200, Thailand ("**the Service Provider**").

hereinafter referred to individually as "a Party" and collectively as "the Parties"

WHEREAS

DNDi's mission is to develop safe, effective and affordable new treatments for patients suffering from neglected communicable diseases and to ensure equitable access to such treatments.

The Service Provider is specializing in the design and implementation of clinical trials and other research projects to improve the management of infectious diseases ("the Field").

DNDi wishes to use certain services of the Service Provider which is willing to provide such services to DNDi for the clinical trial entitled:

Pharmacokinetics of lopinavir/ritonavir superboosting in infants and young children co-infected with HIV and TB

("the Study")

IT WAS THEREFORE AGREED AS FOLLOWS:

1. Definition and provision of the Services:

1.1. Under the terms and conditions hereinafter set out, DNDi hereby appoints the Service Provider for providing the services described in Column A of Annex I hereto ("the Services") and the Service Provider hereby agrees to provide the Services to DNDi by such target dates as set out in Column B of Annex I hereto ("the Target Dates").

1.2. The Service Provider shall provide the Services through its own employees and agents with all care and diligence as usually applicable in the Field and in strict accordance with all applicable laws, regulations and standards.

1.3. Unless otherwise agreed in advance with DNDi in writing, the Service Provider shall not be entitled to sub-contract or assign the performance of any of the Services to any third party.

1.4. The Service Provider agrees that it shall be solely responsible and liable for the consequences of any fault or negligence of any of its employees or agents in providing the Services hereunder and that it shall fully indemnify DNDi, at DNDi's request, for any cost, expense, damage, loss, injury or claim which DNDi or any of DNDi's employees or agents may incur or suffer as a result thereof.

2. Remuneration and Payment Schedule:

2.1. In remuneration for the Services, DNDi shall pay the Service Provider the total amount set out at the bottom of Column C of Annex I hereto (which is inclusive of value added tax or equivalent) and such amount shall be payable in such installments as set out in the same Column.

2.2. Unless otherwise agreed in advance between the Parties in writing, the Service Provider shall not be entitled to get or claim from DNDi any remuneration or payment whatsoever in excess of the total amount set out in § 2.1.

GB

2.3. An advance is paid at the beginning of the contract as set forth in Annex I. Payment is due on presentation of invoices, pursuant to the payment schedule set forth in Annex I, provided that the relevant milestones have been achieved and that DNDi has received satisfactory reports. DNDi shall make the payments within 30 days from receiving the respective invoices that will contain all relevant banking information required for payment. The parties agree that electronic signatures or signatures affixed to any one of the original invoices delivered by facsimile, PDF or other electronic means shall be valid, binding and enforceable.

3. Material (and safety instructions - only if appropriate).

3.1. DNDi will provide the Service Provider with :

- the final version of the protocol, manual of clinical operations, and informed consent form of the clinical trial "HIVPed001";
- the list of study sites, including contact information of the site staff involved in the study;
- a blank set of the final version of the study Case Report Forms, and documented records (e.g. signed form) of verification and validation process;
- ongoing electronic transmission of the Case Report Forms filled out by the study personnel and laboratory results, in PDF or JPEG format with a resolution of 300 dots per inch (DPI);
- answers within 30 days in response to queries regarding the data collected, transmitted by the Service Provider;
- medical information needed to help preparing Serious Adverse Events reports;
- specifications of the datasets to be extracted from the study database maintained by the Service Provider.

For human subjects protection purposes, all patients' data transmitted to the Service Provider will be anonymous and only identified by a code.

3.2. Upon completion of the Services, any remaining material supplied by DNDi will, at DNDi's sole discretion, either be returned to DNDi or destroyed.

GB

4. Intellectual property rights:

All inventions, discoveries, improvements and know-how (whether patentable or not) arising out of, as well as all data, analysis of data, methods and descriptions thereof, information, materials and reports generated through the performance of the Services by the Service Provider under this Agreement ("Results") including without limitation patents, trade secrets and copyright relating thereto shall be vested exclusively in DNDi which shall have the sole and exclusive right to claim and seek legal protection thereupon and to use the same in any manner which it sees fit. To the extent that any Result does not vest automatically in DNDi, the Service Provider hereby irrevocably and unconditionally assigns to DNDi all right, title and interest in and to all such Result, and will execute - and will cause its employees to execute - all documents which may be necessary to give effect to this provision.
This agreement does not include the provision of software.

5. Confidential Information:

5.1. In this Agreement, Confidential Information means any data or information of any kind (whether or not marked 'confidential') in any form or medium which is disclosed, divulged, communicated or made available (whether before or after the date of this Agreement) by DNDi to the Service Provider, irrespective of whether it is in oral or a written form, or recorded or stored by electronic, magnetic, electromagnetic or other form, process or otherwise in a machine readable form or translated from the original language.

5.2. The Service Provider agrees to maintain in confidence all Confidential Information and to refrain, without the prior written permission of DNDi, from (a) using any part thereof for any purpose other than for providing the Services hereunder and (b) disclosing any part thereof to any third party except only to those of the officers, employees and representatives of the Service Provider who shall need to have access to the Confidential Information for the purpose of providing the Services hereunder and who shall be subject to non-use and non-disclosure obligations at least as strict as those set out in this § 5.2.

GB

5.3. The Service Provider shall take at its own cost all reasonable measures to protect all Confidential Information from any loss or damage or any unauthorized use or disclosure and shall be liable for any breach of such obligation by any of its officers, employees or representatives.

5.4. At any time upon request of DNDi for any reason, the Service Provider shall promptly return (and shall cause its officers, employees and representatives to return promptly) to DNDi all Confidential Information in any form, including all copies or extracts thereof in its possession.

5.5. The Service Provider's obligations under this article 5 shall continue after the termination or expiry of this Agreement for a period of three (3) years from the Effective Date.

6. Publications and presentations:

6.1. Subject to the provisions of article 5, DNDi encourages the Service Provider to publish the scientific results of the Services (the "Results") in qualified scientific publications and to present the Results at professional meetings. However, the Service Provider shall not publish or present any part of the Results, including any information and tangible products of any kind whatsoever, without the prior written approval of DNDi to disclose or publish such Results.

6.2. Draft manuscripts of written publications or oral presentations that include any part of the Results shall be sent to DNDi for approval at least twenty-eight (28) days prior to the contemplated presentation or publication. DNDi shall be entitled to amend such draft manuscripts or to object to the proposed publication or presentation on the grounds that it contains or refers to a patentable subject matter. If DNDi makes any such objection, the Service Provider shall refrain from making any publication or presentation for an additional period of sixty (60) days from the date of DNDi's objection in order to allow DNDi to file patent application(s) in such country or countries as DNDi shall decide.

GP

6.3. Unless DNDi advises otherwise, all publications made by the Service Provider related to the Services shall include a notice indicating that DNDi funded the provision of the Services.

7. Records and reports:

7.1. Within four (4) weeks from each Target Date, the Service Provider shall report to DNDi in writing its observations and the Results and shall at the same time send to DNDi a copy of all raw data relating thereto.

7.2. The Service Provider shall retain the Study records for a period of two years after completion or earlier termination of the Study. At the end of this period, the Service Provider will offer to DNDi to retain the reports and data for a longer period at a storage cost to be agreed, to destroy them or to deliver them at DNDi's costs.

8. Contact persons:

8.1. For DNDi :

Marc LALLEMANT
Head of Paediatric HIV Program DNDi
Chemin Louis-Dunant 15
1202 Geneva
Switzerland
Tel: +41 (0)22 90692 30/ + 41 (0)79.293.12.05
Fax: +41 (0)22 90692 34
Email: mlallemant@dndi.org

8.2. For The Service Provider:

AMS-PHPT
Luc Decker
Office: 187/10, Changklan Rd., Changklan, Muang, Chiang Mai 50100, Thailand
luc.decker@phpt.org

9. Relationship between the Parties:

This Agreement is a technical service agreement. It does not and is not intended to create any employer/employee relationship or any partnership between the Parties.

GB

10. Term and termination:

10.1. This Agreement enters into force on the Effective Date and, subject to the provisions of § 10.2, it shall continue until the date of receipt by DNDi of the last written report from the Service Provider as set out in § 7 ("the Term").

10.2. DNDi may terminate this Agreement upon a thirty (30) day written notice given to the Service Provider at any time before the Term and DNDi shall then repay the Service Provider for all justified out-of-pocket expenses incurred or committed by the Service Provider for the Services until the date of receipt of DNDi's notice of termination, as evidenced by vouchers attached to the relevant invoice issued by the Service Provider.

10.3. The obligations mentioned under articles 1.4, 1.5, 4, 5 and 7.2 shall survive expiration or termination of this Agreement, as well as any other obligation which by its nature is intended to survive.

11. Governing Law and Dispute Resolution - Entire Agreement:

11.1. In the event that a dispute arises from or in connection with this Agreement, the Parties shall attempt to settle the matter by amicable means. Should the Parties be unable to achieve resolution, any dispute arising from or in connection with this Agreement, or out of the execution thereof, shall be decided under the rules of the International Chamber of Commerce by one or more arbitrators appointed in accordance with said rules

11.2. The arbitration shall take place in the defendant Party's country. The arbitrator(s) shall be able to read, write and speak English, and the arbitration shall be conducted in English. The arbitral award is final and binding on the Parties, and any Party may apply to a court of competent jurisdiction for enforcement of such award.

11.3. This Agreement including its Annexes constitutes the entire agreement between the Parties as to its subject matter and supersedes any prior oral or written understanding or agreement relating to the same subject matter.

Executed as an Agreement

Authorized Representatives of DNDi

Signature	.....	Signature	.....
Name	Graeme Bilbe	Name	~~Jean-Pierre Paccaud~~
Title	R&D Director	Title	~~Business Dev. Director~~
Date	.....	Date	21/02/2013

Authorized Representative of the Service Provider

Signature	.....
Name	Dr. Wasna Sirirungsi
Title	Dean, Faculty of Associated Medical Sciences
Date	Feb 1, 2013

Annex I - the Services - Target Dates - Payment Schedule

See the Proposal for Data Management Support and the budget detailed in the Data Management bid grid of 3rd September 2012, attached to this Annex I.

A. Description of the Services	B. The Target Dates	C. Total amount in baths and Payment Schedule
Initial advance	Payable 30 days after the signature of the contract by both parties	30% (991,650 baht, includes 99,165 for AMS-CMU overheads)
Preparation of the clinical trial DNDi-HIVPed001 • Participation in the design of Case Report Forms (CRFs) • Design of databases and data dictionaries • Design and development of double data entry systems • Design and development of data verification routines • Design and development of computer tools: system to transmit scanned CRFs; patient monitoring interface.	01 March 2013	10% (330,550 baht, includes 33,055 baht for AMS-CMU overheads)
Data management for Year 1 • Double data entry of Case Report Forms • Data verifications, queries, data corrections • Help preparing Serious Adverse Event reports • Monthly technical progress reports • Provision of datasets	01 December 2013	20% (661,100 baht, includes 66,110 baht for AMS-CMU overheads)
Data management for Year 2 • Double data entry of Case Report Forms • Data verifications, queries, data corrections • Help preparing Serious Adverse Event reports • Monthly technical progress reports • Provision of datasets	01 December 2014	20% (661,100 baht, includes 66,110 baht for AMS-CMU overheads)

GB

End of the study • Final verifications and corrections of the data • Final technical reports (statistics) • Provision of final datasets	01 March 2015	20% (661,100 baht, includes 66,110 baht for AMS-CMU overheads)
		Total amount: 3,305,500 baht

DNDiHIVPed001 Clinical Trial

Proposal for Data Management Support
PHPT, Thailand

In the context of its Pediatric HIV Program, Drugs for Neglected Diseases initiative (DNDi) will conduct a Phase II-III clinical trial in Human Immune Deficiency Virus (HIV) infected children with a recent diagnosis of tuberculosis (TB). The objective of this open label, sequential non-randomized study is to compare the pharmacokinetics of lopinavir when given as lopinavir superboosted with ritonavir (1:1 ratio) combined with rifampicin, or lopinavir boosted with ritonavir (4:1 ratio) without rifampicin in young children (gestational age ≥ 42 weeks and body weight ≤15 kg) . A total of 100 children will be enrolled in 6 South African sites and followed monthly for up to 1 year.

In response to the request for quotation by DNDi on 22 August 2012, PHPT proposes its support to DNDi for clinical data collection and management for the DNDiHIVPed001 study.

PHPT proposes to complete all tasks according to the Terms of Reference detailed below.

1. Task descriptions

- Design of 25 Case Report Forms (paper CRFs), i.e., one 1 or 2 page CRF per category of data such as "demographics", "hematology", "chest x-ray" .... Some CRFs are to be used only once for a case while others are to be used several times (e.g., monthly) during the follow-up. PHPT Data Center will design templates of CRFs and contribute to the adaptation of the templates for the study, and will participate in meetings for CRF discussions and review.
- Design of computerized systems for data collection: development of MySQL relational databases, data dictionaries and data entry interfaces. These data entry systems will only be used internally at PHPT.
- Tracking of study records: setup and maintain databases storing references of completed CRFs, enrolled patients and dates of completed visits.
- Double data entry of the completed Case Reports Forms. About 200 Case Report Forms pages are expected be filled for each subject over the 12 month follow-up period of each patient (total number of paper forms to be keyed = 20,000 pages (+ or - 10%).
- Filing of Case Reports Forms, tracking of corrections/changes
- Data management: (1) systematic verification of all collected data using automated computer tools able to detect inconsistent, abnormal or missing values; these tools will be developed at PHPT using a Stata statistical software; (2) issuance and follow-up of data queries (*requests for corrected or missing data*); (3) correction of databases with tracking and documentation of the changes.
- PHPT research nurses will help preparing Serious Adverse Event reports; a secured web interface will be provided to allow viewing and editing reports remotely.
- Preparation of monthly and final technical progress reports.
- Preparation and transmission of the datasets to the research team at DNDi.
- Answering requests from the DNDi research or statistics team.

GD

2. Deliverables

PHPT Data Center will provide the following items:

- Main objective: datasets ready for statistical analysis, verified for inconsistent, abnormal or missing data. These datasets will be provided in Stata format (every 6 months and for interim analysis).
- Data dictionaries: description of all datasets, variables and codes.
- Documentation of the Data Management activities: a Data Management manual listing of data verification criteria; database providing an audit track for the corrected data.
- Monthly and final progress reports with detailed descriptive statistics.
- Real-time alert messages in case of safety issues (e.g., grade 4 laboratory results), triggered at the data entry level. Software developed at PHPT will automatically send e-mails to the medical team, according to customized safety criteria.
- "Patient Monitoring software": a real-time access to the subject data already recorded in databases, through a web interface and user friendly screens separated by type of data/laboratory results.

3. Relationships between PHPT Data Center and DNDi

- The DNDi Pediatric HIV research team provides the study protocol, manual of operations and finalized Case Report Forms to PHPT Data Center.
- The South African sites transmit the completed Case Reports Forms to PHPT Data Center (see "Logistics" below).
- PHPT will send queries to the study sites if possible wrong data are detected; the sites are responsible to answer to these queries within one month.
- PHPT will provide datasets to the DNDi research team.
- PHPT will answer to requests from DNDi related to any data quality issue; PHPT will provide an electronic form as a recommended method for the collection and processing of these requests.
- All communications between PHPT, the sites and DNDi will be in English.

4. Timing

- The Databases and Data Entry systems created by the PHPT Data Center will be ready to operate within 7 weeks after signature of a contract between PHPT and DNDi *and* transmission of the finalized Case Report Forms.
- The "Patient Monitoring Program" will be ready for use within 10 weeks after signature of the contract.
- After data collection is started, the PHPT Data Center will prepare and send every month a technical progress report of the study (created by Data Managers and Statisticians) to DNDi.
- After completion of the enrollment and data collection on site, the PHPT Data Center will send a final technical report with descriptive statistics within 3 months.

5. Logistics

- PHPT has a long experience in developing and maintaining web-based software, allowing remote access to the databases and user interfaces. The distance between the study sites in South Africa and the PHPT Data Center will not impact the course of the study and the efficiency of the data collection.
- We propose that Case Report Forms will be filled as paper forms, at the study sites in South Africa, and then transmitted weekly to the PHPT Data Center in electronic format after being scanned with a resolution of 300dpi. The documents will saved as digital pictures or PDF files. A secured web interface will be set-up for the transmission of the electronic files to PHPT.

GB

- PHPT data managers will issue and transmit data queries to the South African sites, though electronic forms.

6. Capacities and competencies

PHPT Data Center has the capacity and experience in conducting similar assignments under strict compliance with the Good Clinical Practice (ICH E6) standard, and with the regulations related to the Protection of Human Subjects.

The Data Center is currently organized with 8 Data Managers, 5 Data Entry Technicians, 2 Statisticians, 2 Analyst-Programmers, one Database Administrator and one computer technician. Evidence of staff competency and trainings (biosketches) and samples of previous work are available on request.

The PHPT Research Unit has been working on HIV research since 1996, conducting several major studies (phase II and III clinical trials). The Unit is setup as a CTU for the IMPAACT network as well as the PENTA network. A cohort of patients is followed since 2003, under funding of the *Global Fund To Fight Aids, Tuberculosis and Malaria*, with currently over 2000 patients including 600 children.

PHPT works under a Quality Management System certified ISO-9001 by "Bureau Veritas" since 2008 (attached certificate).

GB