21. OVERVIEW: ANCILLARY STUDY PROPOSALS, SECONDARY DATA ANALYSIS REQUESTS AND REQUESTS FOR DATASETS

Any proposed research that makes use of data, biological specimens or other information from a Microbicide Trials Network (MTN) study is subject to administrative approval by the MTN and, if applicable, regulatory approval by the U.S. National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS). This research includes the following:

- Ancillary study: an investigation not described in the original protocol that requires new data collection or additional lab sample analyses.

- Secondary data analysis: an analysis by the Statistical and Data Management Center (SDMC) of existing qualitative and/or quantitative study data collected in a MTN study for the purposes of writing an abstract, manuscript or other scientific publication and/or for presenting at a meeting or conference by an investigator not on the protocol team.

  Note: requests by protocol team members should follow the publication approval process, as described in Section 20 of this manual.

- Request for MTN dataset: a request for data by a researcher who wants to conduct his or her own analysis. This does not apply to dataset releases for purposes of conducting protocol-specified primary and/or secondary endpoint analyses (for example, Audio/Computer Assisted Self Interview [A/CASI] dataset releases to the MTN Behavioral Research Working Group [BRWG]). It also does not apply to dataset releases to study sponsors for purposes of regulatory submissions (e.g., for preparation of Clinical Study Reports).

  Note: requests for dataset releases for protocol-specified primary and/or secondary endpoint analyses should follow the publication approval process, as described in Section 20 of this manual.

The purpose of the review and approval process (outlined in Table 21.1) for ancillary studies, secondary data analysis requests and requests for datasets is to ensure that MTN and Clinical Trials Unit (CTU) resources are used appropriately and that the rights and well-being of human subjects are protected in accordance with the U.S. Code of Federal Regulations (CFR) 45 CFR 46, which can be accessed at the following website: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html.

An MTN investigator or non-MTN investigator may propose an ancillary study, request a secondary data analysis or request a dataset. This investigator is responsible for ensuring that all necessary regulatory and administrative approvals are obtained and all relevant MTN and NIAID/DAIDS procedures are followed.

Ancillary studies, secondary analyses and creation of datasets may involve the use of MTN supplemental funding, funding from other sources or a combination of these. The proposed source(s) of funding must be specified in the Ancillary Study Application, Secondary Data Analysis Request Form, or Dataset Request Form. If any MTN funding is needed, the MTN Executive Committee (EC) will determine if and how these funds may be made available.

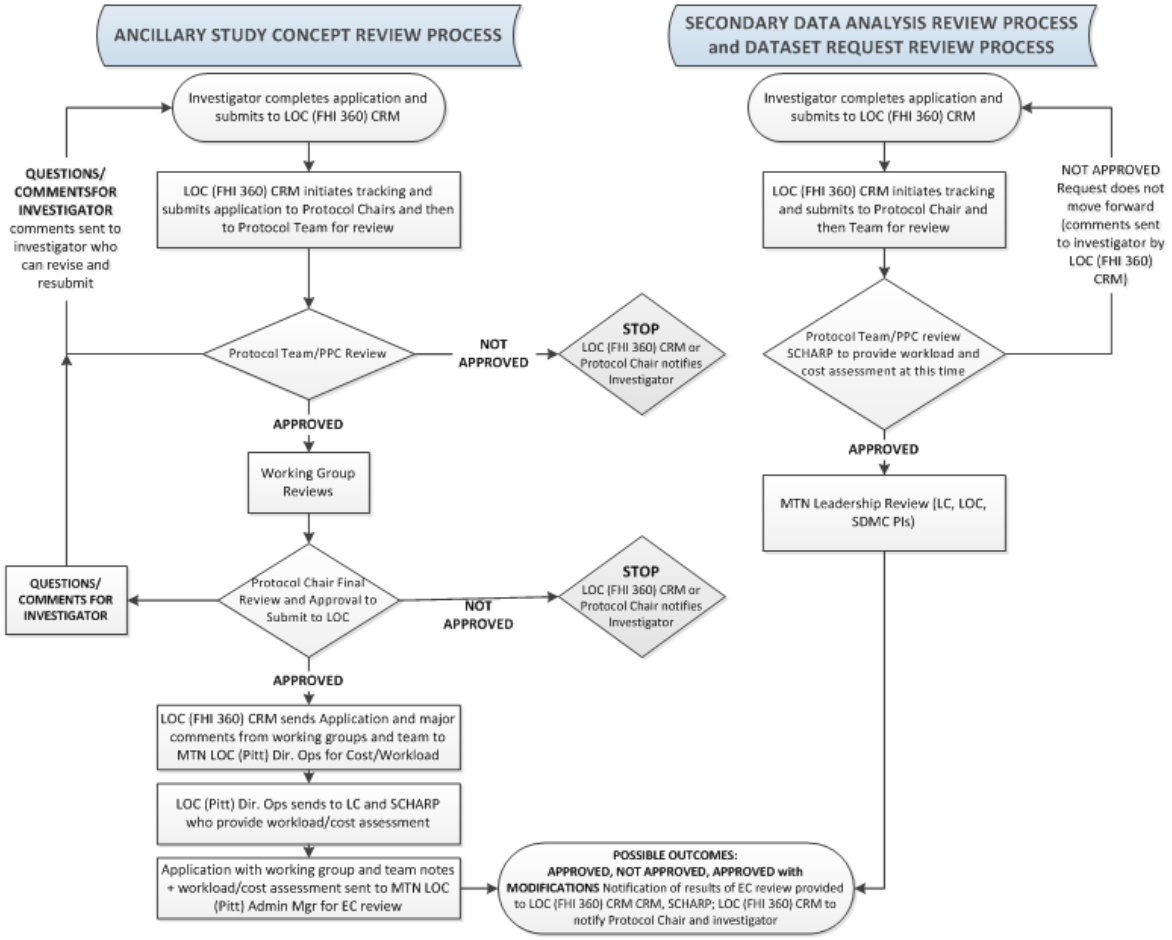
Please refer to Table 21.1 and Figure 21.1 below to determine the appropriate process to follow for each type of request as well as its corresponding section within the MOP.

Table 21.1. Applicable MOP Sections for MTN Data Publication, Ancillary Study, Secondary Data Analysis, and Dataset Requests: Where to Look

	Publication Process (MOP Section 20)	Ancillary Study Request Process (MOP Section 21.1)	Secondary Data Analysis Request Process (MOP Section 21.2)	Dataset Request Process (MOP Section 21.3)
Are you requesting SDMC analysis of study data and are a member of the study Protocol Team?	X			
Are you requesting SDMC analysis of study data, but are *not* a member of the study Protocol Team?			X	

Are you requesting approval for new data collection, data abstraction from participant records (for data that is not in the study database), or additional analyses done on lab specimens?		X		
Are you requesting a dataset (no analysis by SDMC needed) for purposes of conducting protocol-specified primary and/or secondary endpoint analyses (e.g., A/CASI dataset releases to the MTN BRWG)?	X			
Are you requesting a dataset (no analysis by SDMC needed) to conduct your own analyses *outside* of what is specified in the protocol for primary and secondary endpoint analyses?				X

Figure 21.2. Flowchart of Ancillary Study Concept Review, Secondary Data Analysis Review, and Dataset Request Review Process



21.1 Ancillary Studies

Ancillary studies are defined as investigations that are not described in the original protocol and *require additional data collection or sample analyses to be performed*. They can be either retrospective or prospective in nature. Examples of ancillary studies include studies that require analyses of biological specimens, collection of additional specimens, or the administration of behavioral surveys or focus group discussions.

21.1.1 MTN Review and Approval of Ancillary Studies (Administrative)

The administrative actions for approval of an ancillary study proposal are described below. For ancillary studies involving multiple MTN protocols, the Leadership and Operations Center (LOC) (FHI 360) designates one Clinical Research Manager (CRM) to lead the process simultaneously for each applicable protocol, as outlined below.

Completion of an Ancillary Study Application: A proposing investigator must complete an Ancillary Study Application, (http://www.mtnstopshiv.org/resources), and, if the investigator

plans to use specimens stored from completed MTN clinical trials, a MTN Materials Transfer Agreement (MTA) form (http://www.mtnstopshiv.org/resources) must also be completed. The MTN Ancillary Study Application requires a short description of the proposal explaining the rationale; scope of work and requirements (for example, materials, laboratory assays, statistical support, staff resources or specimen shipping); estimated costs; and proposed or potential source(s) of funding.

Proposing investigators are responsible for compiling all estimated costs and including the total budget in the MTN Ancillary Study Application. In developing this budget, the proposing investigators should obtain cost estimates from the Principal Investigator (PI) (or other lead investigator) of each collaborating organization that has been proposed to take part in the study (for example, the study sites, the LOC, SDMC and the Laboratory Center [LC]). The MTN MTA should be sent directly to the MTN LOC (University of Pittsburgh [Pitt]) Administrative Manager via the alias list mtnadmmgr@mtnstopshiv.org. The proposing investigator submits the completed Ancillary Study Application to the LOC (FHI 360) CRM for the primary study.

Initial Review by the Protocol Team/Protocol Publications Committee (PPC): Once the proposing investigator submits the completed Ancillary Study Application to the LOC (FHI 360) CRM for the primary study, the LOC (FHI 360) CRM will circulate the application to the Protocol Chair(s), and if approved by the Protocol Chair(s), to the protocol team. At this point, the LOC (FHI 360) CRM will initiate tracking of the review process. The protocol team is asked to provide comments regarding the Ancillary Study Application. Ideally, the entire protocol team will provide comments, but at a minimum, comments must be received from the PPC, which includes the Protocol Chair(s), the Protocol Statistician, the DAIDS Medical Officer (MO), and the MO from any other relevant funding agencies (such as the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development [NICHD] for collaborative studies between the Adolescent Medicine Trials Network [ATN] and MTN). The proposal may be discussed with the protocol team or PPC members either during a conference call or via email. The PPC decides one of three things: (i) to move the Ancillary Study Application forward in the review process, (ii) to request modifications to the application (by the investigator) or (iii) not to approve the application. The CRM will provide written feedback from the PPC to the investigator who submitted the Ancillary Study Application.

Scientific Review by MTN Working Groups: If the PPC approves the Ancillary Study Application, the LOC (FHI 360) CRM will send the completed Ancillary Study Application and written documentation of the PPC's initial review and feedback to MTN Working Groups (WG) (the BRWG, the Biomedical Sciences Working Group and the Community Resource Working Group) and to external experts, as applicable. This communication should include the PPC's assessment of the strengths and weaknesses of the application, as appropriate. Collectively, the WGs will be offered an opportunity to provide input within a set time frame to supplement the review by the protocol team.

Final Review by the Protocol Chair(s): The Protocol Chair(s) will make a final decision, based on the recommendations of the MTN WGs and the PPC, whether to: (i) approve the application as written and submit the Ancillary Study Application to the MTN EC for review; (ii) request that the proposing investigator make revisions and re-submit a revised Ancillary Study Application; or (iii) reject the application. The Protocol Chair(s) or the LOC (FHI 360) CRM will notify the investigator of the decision.

If the Ancillary Study Application is approved by the Protocol Chair(s), the LOC (FHI 360) CRM will submit the Ancillary Study Application with notes summarizing the key points of the reviews

by the PPC, as well as the WGs, to the MTN LOC (Pitt) Administrative Manager (mtnadmmgr@mtnstopshiv.org), who in turn will request a workload and cost assessment from the LC and SDMC. Once the MTN LOC (Pitt) Administrative Manager receives the requested workload and cost estimates, s/he will send these, along with the application and summary notes from the LOC (FHI 360) CRM, to the MTN EC with a request that the MTN EC review and vote on the concept. If the Protocol Chair(s) is not willing to move the concept forward based upon input from the WGs, the Protocol Chair(s) or LOC (FHI 360) CRM must communicate its decision, in writing, to the investigator who submitted the application.

In the event that the investigator is not satisfied with the decision, s/he can make an appeal to the MTN EC by notifying the LOC (FHI 360) CRM, who will then refer the request to the MTN LOC (Pitt) Administrative Manager (mtnadmmgr@mtnstopshiv.org).

Review by the MTN Executive Committee: Once the Ancillary Study Application is approved by all required parties and submitted to the MTN LOC (Pitt) Administrative Manager (mtnadmmgr@mtnstopshiv.org), it will be added to the agenda for the next MTN EC meeting or call. At the meeting or call, the MTN EC will review the concept application and all relevant materials and vote on the application. The EC review will result in three possible outcomes: approved, not approved, or approved with modifications and guidance on next steps, as needed. The EC will also determine whether approval by a relevant Investigational New Drug (IND)-holder and/or Product Developer is required. Finally, the EC will determine the proposal's relative priority vis-à-vis other Network priorities. The SDMC PI, who is a member of the EC, communicates the priority ranking to the statistical staff. The MTN Director of Operations or the MTN LOC (Pitt) Administrative Manager communicates the outcome of the EC review to the LOC (FHI 360) CRM, who in turn communicates the outcome and relative priority to the proposing investigator and Protocol Chair(s).

21.1.2 Regulatory Approval for Ancillary Studies

Ancillary studies conducted with supplemental MTN funding are subject to DAIDS regulatory approval. Similar approvals also may be required by other funding agencies (for example, NICHD for collaborative studies between the ATN and MTN). Investigators will work with the LOC (Pitt) Protocol Development Manager and DAIDS MO to determine which approvals are required, which may vary depending on the scope and nature of the study. These may include the following:

DAIDS Prevention Science Review Committee (PSRC) Review: The DAIDS MO, in collaboration with the DAIDS Chief of the Clinical Microbicide Research Branch and the PSRC Chair, determines if a PSRC review is required.

Informed Consent Considerations: Proposing investigators work with the LOC (Pitt) Protocol Development Manager and DAIDS to determine whether separate informed consent is needed, which will depend on the ancillary study's design and study procedures and the language included in the informed consent forms (ICF) for the primary study. For example, a separate ICF would be required if the ancillary study involves additional procedures, specimens or visits and/or involves risks and benefits that are different from those described in the primary study.

If the ancillary study requires a separate ICF and MTN funding is used for the investigation, the sample ancillary study ICF must be submitted to the DAIDS Regulatory Support Center (RSC) for review and approval prior to submitting the site-specific ICFs to the responsible Institutional Review Boards/Independent Ethics Committees (IRBs/IECs). Ancillary study ICFs must comply

with U.S. federal requirements, as outlined in 45 CFR 46. The ICF template used for MTN studies should serve as a guide for ancillary study ICFs. After the RSC has approved the sample ICF, site-specific versions must be prepared, including translations into local languages and independent back-translations (when applicable), for submission to the responsible IRBs/IECs. Further details on this process are provided in Section 11.2 of this manual.

Documentation of IRB/IEC Approval or Exemption: Documentation of all IRBs/IECs submissions, as well as approvals and/or determinations of exemption under 45 CFR 46, must be submitted to the LOC (Pitt) Regulatory Group.

Site-Specific Registration of Ancillary Studies: If the ancillary study uses supplemental MTN funding and requires separate informed consent, participating study sites may be required to complete protocol registration procedures with the DAIDS RSC. Procedures and requirements for protocol registration are detailed in the *DAIDS Protocol Registration Policy and Procedures Manual* and Section 11.3 of this manual. For ancillary studies that require protocol registration, no ancillary study activities may be initiated until the RSC has notified the site in writing that all registration requirements have been met.

21.1.3 Monitoring Ancillary Studies

An ancillary study funded by MTN may be monitored by the DAIDS Clinical Site Monitoring Group (CSMG), if specifically requested by DAIDS. If DAIDS decides not to require CSMG monitoring of the ancillary study, other quality assurance procedures may be implemented for the study at the discretion of the proposing investigators and/or the MTN EC.

21.1.4 Management and Analysis of Ancillary Study Data

Plans for handling ancillary study data must be specified in the Ancillary Study Application. Prior to submitting the application, investigators are required to discuss plans for data collection, management and analysis with the SDMC PI (or other SDMC representative designated by the SDMC PI) to clarify what SDMC input and/or access to primary-study data will be needed. The SDMC may or may not assume responsibility for handling ancillary data.

21.1.5 Documentation of Approvals of Ancillary Studies

Copies of all MTN, regulatory and IRB/IEC approvals (if applicable) must be maintained on file by the lead ancillary study investigator and by each participating study site and sent to the LOC (Pitt) Regulatory Group, as requested.

21.1.6 Requirements for Using Stored Biological Specimens

In addition to the requirements described above, specific requirements apply to ancillary studies that use stored biological specimens. These requirements apply to all MTN investigators and other staff members, as well as non-MTN investigators involved in testing specimens that are collected and stored for possible future research testing in MTN studies. (Refer to Section 14.7 of this manual for additional information.) Additional requirements for use of stored specimens are as follows:

- Protocol-specified study endpoints will receive the highest priority.

- Specimens may not be used for ancillary studies until the LC and SDMC have confirmed that all protocol-specified testing for the primary study has been completed, results have been received and any associated data queries have been resolved, unless the LC and SDMC agree to an exception from this requirement.

- Prior to shipping or using specimens for an ancillary study, sites must confirm that the participant consented to long-term storage and possible future research testing of the specimens, and that the consent obtained is consistent with the objectives of the ancillary study. Otherwise, specimens may not be used for the ancillary study unless additional consent is obtained specifically for the ancillary study.

All investigators proposing to test stored specimens must complete an MTN MTA (http://www.mtnstopshiv.org/resources) and attach a copy of the signed agreement to the Ancillary Study Application.

21.1.7 Publication of Results of Ancillary Studies

Data analyses, presentations and publications resulting from ancillary studies will be prepared and reviewed in accordance with relevant DAIDS and MTN policies. Specifically, any abstracts or manuscripts developed using data obtained via an MTN-approved ancillary study must undergo the publication process described in Section 20 of this manual, with the exception that no concept submission is required because the ancillary study was already approved. For example, the first step in Table 20.1 “Review of concept publication by PPC” is skipped.

21.2 Secondary Data Analyses

Note: *This section applies only to proposed secondary data analyses made by investigators who are not on the protocol team of the protocol for which data analysis is requested. Protocol team members with proposed secondary data analyses should follow the MTN publication process, as specified in Section 20 of this manual.*

Secondary data analyses are analyses of existing qualitative and/or quantitative data collected in a MTN study to address a new research question proposed by an investigator who is not on the protocol team. These analyses are retrospective in nature, involving data that was collected previously as part of an MTN trial and that does not require additional procedures or analyses of specimens. Additional statistical support from the SDMC is often necessary. Secondary data analyses are subject to MTN’s approval.

For secondary analysis requests involving multiple MTN protocols, the LOC (FHI 360) designates one CRM to lead the process simultaneously for each applicable protocol, as outlined below and depicted in Figure 21.1.

21.2.1 MTN Review and Approval of Secondary Data Analysis Requests

Completion of Secondary Data Analysis Request Form: Proposing investigators must complete a Secondary Data Analysis Request Form (http://www.mtnstopshiv.org/resources). The form requires a short description of the proposed investigation explaining the rationale, objectives, methods, necessary staff and other resources, and other relevant information.

Review by the Protocol Team/PPC: The proposing investigator submits the completed Secondary Data Analysis Request Form to the LOC (FHI 360) CRM for the protocol. The LOC (FHI 360) CRM will send the form to the Protocol Chair(s), and if approved, to the protocol team, who are asked to provide comments. Ideally, the entire protocol team will provide comments, but at a minimum, comments must be received from the PPC. The proposal may be discussed by the protocol team or PPC members either during a conference call or via email. At this stage of review, the SDMC should provide the PPC with a workload and cost assessment for the analysis request. The PPC decides one of three things: (i) to move the request forward in the review process, (ii) to request modifications to the request (by the investigator), (iii) or not to approve the request. The LOC (FHI 360) CRM will provide written feedback from the PPC to the investigator who submitted the Secondary Analysis Request Form.

If the PPC approves the request, the Protocol Chair(s) or LOC (FHI 360) CRM submits the request, the workload and cost assessment to the MTN LOC (Pitt) Administrative Manager (mtnadmmgr@mtnstopshiv.org) for review by the MTN Leadership Group.

Review by the MTN Leadership Group: After Proposed Secondary Analysis Requests are approved by the PPC, they are reviewed by the MTN Leadership Group. The MTN Leadership Group may decide to include members of the MTN EC in their review. The MTN Director of Operations or the MTN LOC (Pitt) Administrative Manager communicates the outcome of the review to the LOC (FHI 360) CRM, who in turn communicates the outcome to the proposing investigator and Protocol Chair(s). If the MTN Leadership Group approves the request, it will determine whether approval from a relevant IND holder and/or Product Developer is required. The MTN Leadership Group will also determine the request's relative priority vis-à-vis other Network priorities. The SDMC PI, as a member of the Leadership Group, communicates the priority ranking to the statistical staff. The MTN Director of Operations or the MTN LOC (Pitt) Administrative Manager communicates the outcome of the Leadership Group review to the LOC (FHI 360) CRM, who in turn communicates the outcome and relative priority to the proposing investigator and Protocol Chair(s).

21.2.2 Publication of Results of Secondary Data Analyses

Any presentations or publications that rely on secondary data analyses will be prepared and reviewed in accordance with relevant DAIDS and MTN policies. Specifically, any abstracts or manuscripts developed using study data obtained via an MTN-approved secondary data analysis must undergo the publication process described in Section 20 of this manual, with the exception that no concept submission is required because the secondary analysis was already approved. For example, the first step in Table 20.1 "Review of concept publication by PPC" is skipped.

21.3 Requests for Datasets

Requests for datasets are occasionally made by investigators who wish to conduct their own analyses (for example, a PhD thesis) outside of the protocol-specified primary and secondary endpoint analyses. The process by which requests for datasets are reviewed and approved is described below. For dataset requests involving multiple MTN protocols, the LOC (FHI 360) designates one CRM to lead the process simultaneously for each applicable protocol, as outlined below.

For approved requests by investigators outside of the MTN, a Data Transfer Agreement must be in place for the SDMC to release the applicable dataset(s) to the proposing investigator. The SDMC will work directly with the proposing investigator to draft and finalize the Data Transfer Agreement.

21.3.1 MTN Review and Approval of Requests for Datasets

Completion of Dataset Request Form: Proposing investigators must complete a Dataset Request Form (http://www.mtnstopshiv.org/resources). The form requires a short description of the proposed investigation explaining the rationale; objectives; methods; necessary staff and other resources, and other relevant information.

Review by the Protocol Team/PPC: The investigator requesting a dataset will submit a completed Dataset Request Form to the LOC (FHI 360) CRM for the protocol.

The LOC (FHI 360) CRM will send the form to the Protocol Chair(s), and if approved by the Protocol Chair(s), to the protocol team, who are asked to provide comments. Ideally, the entire protocol team will provide comments, but at a minimum, comments must be received from the PPC. The proposal may be discussed by the protocol team or PPC members either during a conference call or via email. At this stage of review, the SDMC should provide the PPC with a workload and cost assessment for the dataset request. The PPC decides one of three things: (i) to move the request forward in the review process, (ii) to request modifications to the request (by the investigator), or (iii) not to approve the request. The LOC (FHI 360) CRM will provide written feedback from the PPC to the investigator who submitted the Dataset Request Form.

If the PPC approves the request, the Protocol Chair(s) or LOC (FHI 360) CRM submits the request, the workload and cost assessment to the MTN LOC (Pitt) Administrative Manager (mtnadmmgr@mtnstopshiv.org) for review by the MTN Leadership Group.

Review by the MTN Leadership Group: After the PPC approves the proposed dataset request, it is reviewed by the MTN Leadership Group. The MTN Leadership Group may decide to include members of the MTN EC in their review. This review will determine whether the dataset can be released and whether approval is required from a relevant IND holder and/or Product Developer. The MTN Leadership Group will also help to set priorities for the work required of the SDMC by informing the SDMC of the relative priority for this work, given other ongoing projects. The MTN Director of Operations or the LOC (Pitt) Administrative Manager communicates the outcome of the review to the LOC (FHI 360) CRM, who in turn communicates the outcome to the proposing investigator and Protocol Chair(s). The SDMC PI communicates the priority ranking to the statistical staff. These established priorities are included in communications to the proposing investigator, Protocol Chair(s) and LOC (FHI 360) CRM regarding the outcome of the review.

21.3.2 Publication of Results of Request for Datasets

All data analyses, presentations and publications resulting from research funded by MTN will be prepared and reviewed in accordance with relevant DAIDS and MTN policies. This includes work relying on MTN data sets. Specifically, any abstracts or manuscripts developed using study data obtained via an MTN-approved dataset request must undergo the publication process described in Section 20 of this manual, with the exception that no concept submission is required. For example, the first step in Table 20.1 “Review of concept publication by PPC” is skipped.