# Standard Operating Procedures forModus Operandi and Communication with the Clinical Advisory Committee

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| **SOP Number**: SP-024-CT  | **Effective Date**:  |
| **Version Number and Date**: 2.0, Date 02-Sep-2019 |

**Table of contents**

[1. PURPOSE 2](#_Toc166244889)

[2. SCOPE 2](#_Toc166244890)

[3. RESPONSIBLE FUNCTIONS 2](#_Toc166244891)

[4. DEFINITIONS and ABBREVIATIONS 2](#_Toc166244892)

[5. PROCEDURE 3](#_Toc166244893)

[5.1 When the site should contact the CAC? 3](#_Toc166244894)

[5.2 Flow of requests for advice 3](#_Toc166244895)

[5.3 Subject Line of the Email Query to CAC 4](#_Toc166244896)

[5.4 Supporting Information to the Email Query 4](#_Toc166244897)

[5.5 Decision making process 5](#_Toc166244898)

[5.6 Feedback from the CAC to the site PI 5](#_Toc166244899)

[5.7 Composition 5](#_Toc166244900)

[6. REFERENCES 5](#_Toc166244901)

[7. SUPPORTING DOCUMENTS 6](#_Toc166244902)

[8. APPENDIX 6](#_Toc166244903)

# Standard Operating Procedures for*Modus operandi* and Communication with the Clinical Advisory Committee

## PURPOSE

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| This standard operating procedure (SOP) describes the functioning of the Clinical Advisory Committee (CAC) and the procedures that the endTB Clinical Trials sites should follow to request recommendations from the Clinical Advisory Committee. |

## SCOPE

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| This SOP aims to describe how the Clinical Advisory Committee (CAC) receives, reviews, and answers questions sent by the site PIs of endTB Clinical Trials and how they shall communicate with the CAC to ensure prompt answers to questions regarding clinical management of study participant(s). |

## RESPONSIBLE FUNCTIONS

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| **Function** | **Activities** |
| **Site Principal Investigator (Site PI) and/or delegated Site Co-Investigator (Site CI)** | * Generates queries for the CAC.
* Communicates queries to the CAC.
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| **Site Study Coordinator (Site SC)** | * Communicates queries to the CAC on behalf of the Site PI or delegated Site Clinical Investigator(s).
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| **Clinical Advisory Committee (CAC): permanent members and external experts** | * Gives quick answers to any clinical questions sent by the site
* Supports the Event Validation Group
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| **Central Study Coordinator and/or Trial Manager and/or Quality Assurance Officer** | * Supports CAC to liaise with sites when needed
 |

## DEFINITIONS and ABBREVIATIONS

**Clinical Advisory Committee (CAC):** The CAC is composed of both internal and external clinical experts representing various disciplines and specialties. It serves as an advisory body to endTB site investigators by providing consultation regarding subject eligibility, case management, medical monitoring, and permanent treatment discontinuation.

## PROCEDURE

### When the site should contact the CAC?

The role of the CAC is to provide advice to study sites in five main circumstances:

1. Eligibility: **Site PI** may ask advice from the CAC if they have questions or doubts about the eligibility of a patient, including review of exception of exclusion criterion 5b in endTB Clinical Trial (has received second-line drugs for 15 days or more prior to screening visit date).
2. The CAC must be consulted before any permanent regimen change [addition, discontinuation, or replacement of investigational drug(s)] is made. Temporary suspension does not require consultation. Permanent investigational drug dose changes may also be discussed with the CAC. Permanent discontinuation may be considered in the following circumstances:
	* Serious toxicity (see SOP ***SP-018-CT*** on ***Management of Specific Adverse Events***);
	* Required use of prohibited concomitant medication (See SOP ***SP-019-CT*** on ***Concomitant Medications***);
	* Any condition (social or medical) which, in the opinion of the **Site PI** would make the study participant unsafe;
	* Positive culture at week 16 or later;
	* When the clinician has an indication of a treatment failure, poor response, or recurrence (see SOP ***SP-028-CT*** on ***Management of Early Termination***).
3. Construction of a standard of care drug regimen. This may be for trial patients at time of initial regimen design or following an update of WHO recommendation for MDR-TB treatment, or for a patient referred from the endTB Clinical Trials to local routine care.
4. Management of difficult cases (co-morbidities, adverse events, etc.).
5. Review **Site PI** recommendations for patients becoming pregnant, when approved in the country.

The CAC may also support the Event Validation Group in outcome assignment whenever needed and in particular in cases requiring evaluation of bacteriological, radiographic and clinical evolution (see SOP ***SP-031-CT*** on ***Event Validation*** and ***SP-032-CT*** on ***Evaluating bacteriological, radiographic and clinical evolution for outcome classification***).

### Flow of requests for advice

Requests for advice/questions from the site trial staff should be sent by the **Site PI**, **Site CI** or **Site SC** on behalf of the Site PI, in English, to the **permanent CAC member** address:

endTB.cac@paris.msf.org

* The **permanent CAC members** will define on-call period.
* The **on-call** **permanent CAC member** will receive the request (refer to section 5.5); will verify that the documentation provided by the **Site PI** or **delegate** and formulation of the query are complete and clear; if this is not the case, s/he will write back to request additional information.
* If needed, and with the help of the **Central Study Coordinator and/or Trial Manager and/or Quality Assurance Officer**, the **on-call** **permanent CAC member** will distribute and track queries to external expert(s) and to the **other** **permanent CAC member**.

### Subject Line of the Email Query to CAC

**Site PI, delegated Site CI** or **Site SC** must classify the email query according to the three categories below and label the subject line of the email query accordingly:

* **endTB CAC request: [Patient ID] - New** – for new question
* **endTB CAC request: [Patient ID] [Issue]- FU** – for follow-up issues
* **endTB CAC request: [Patient ID] [Issue] – URGENT** – ONLY for emergency query that must be answered as soon as possible. This should be used for any urgent issue aroused from a trial patient that is about to be randomized, any urgent decision to be made for the safety of a trial patient, or any urgent decision regarding treatment discontinuation of a trial patient.

### Supporting Information to the Email Query

**Site PI** or **Site CI** must detail the essential information of the trial patient, the clinical question, and the list of patient’s concomitant medications by using the CAC request form in Appendix A2. Both word or pdf format are acceptable for the form. Requests should be sent in English.

Simple queries, such as protocol clarifications (e.g. less than one paragraph of text), can be sent by email. If further details are requested by the CAC, the CAC request form should be completed.

**Site PI** or **Site CI** must follow the instructions below to complete the CAC request form:

Page 1 (P.1) must be completed for all queries

* General subject information should be chronological, synthesised and focused on the main issue:
	+ If the main issue is about the absence of clinical improvement or clinical worsening, report the baseline clinical findings and if there was improvement in between.
	+ If the question is about drug toxicity, always report baseline or previous finding. The CAC needs to be able to appreciate the clinical evolution.
	+ Report of clinical finding or vital signs must be concise. For example, do not report “fever” but the value body temperature. In case of adverse event, report the grading.
	+ For non-TB test results, always report the date of sample collection.
* Question to the CAC should be concise and precise.
* Indicate applicable attached documents.

Page 2 (P.2) shall be completed only if the query concerns clinical management or treatment change

* MDR-TB treatment:
	+ Specify date treatment started and daily dosage (mg), change of dosage, and cessation of drugs from prior to study treatment initiation (randomization) to present.
	+ Fill a new row only if there was a change in treatment: addition of a drug, interruption of a drug or change of dosage. For any change, add in comment the main cause: safety, refusal, DST.
	+ In case of safety or refusal, give more detail in the narrative on Page 1.
* Bacteriology: report the available smear (0, scanty, +, ++, +++) and culture results (P: positive; N: negative; C: contaminated) based on the date of sample collection.
* Drug susceptibility results: specify test sample collection date and result:
	+ R = resistant
	+ S = susceptible
	+ C = contaminated
	+ N = negative
* Report the body weight for each sequential visit. In comment for the first row, add the patient Height, in case the CAC needs to calculate the BMI.
* Use the comment box to add information about poor adherence or missing drugs.

**Site PI** or **Site CI** shall update the CAC request form with the most current information on the trial patient’s culture and/or drug susceptibility test (DST) results, anti-TB and other concomitant medications, demographic data, and other relevant clinical information.

**Site PI** or **Site CI** shall update the CAC of the final decision.

### Decision making process

* The on-call **permanent** **CAC member** may convene teleconferences with the **other permanent CAC membe**r, **site PIs**, and/or **CAC specialists** as needed.
* The **on-call permanent CAC** **member** provides recommendations within 3 business days for regular requests and within 24 hours for urgent requests, as defined by the subject line (refer to section 5.3).

### Feedback from the CAC to the site PI

The **on-call permanent CAC member** will communicate the final answer to the **Site PI**, the corresponding **Central Study Coordinator** and **Site SC**, and ensure that the **Site PI** acknowledge receipt and file the correspondence. Site will print the final answer and file it in the patient medical file.

### Composition

The committee is composed of **permanent CAC members**, and **external experts** who can be contacted *ad hoc.* The **Central Study Coordinator and/or Trial Manager and/or Quality Assurance Officer** can also be solicited as needed to facilitate (see Appendix A1).

The **CAC members** commit to providing answers in due time (3 business days after they accept to review a regular request, 24 hours for an urgent request) and to participate in teleconferences if necessary.

If the **CAC members** detect any trend of similar query(ies) or request(s) submitted from different sites or concerning the same study issue, an ad hoc CAC meeting could be called to discuss the trend and to propose appropriate plan of actions.

## REFERENCES

None

## SUPPORTING DOCUMENTS

* SOP SP-018-CT Management of Specific Adverse Events (endTB Site Study Documents)
* SOP SP-019-CT Concomitant Medications (endTB Site Study Documents)
* SOP SP-028-CT Management of Early Termination (endTB Site Study Documents)
* SOP SP-031-CT Event Validation (endTB Site Study Documents)
* SOP SP-032-CT Evaluating bacteriological, radiographic and clinical evolution for outcome classification (endTB Site Study Documents)

## APPENDIX

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| **Number** | **Title** |
| A1 | SP-024-CT\_A1-Clinical Advisory Committee Contact list |
| endTB A2endTB-Q A2 | SP-024-CT\_endTB A2-Clinical Advisory Committee Request FormSP-024-CT\_endTB-Q A2-Clinical Advisory Committee Request Form |