# Standard Operating Procedures for

# Concomitant Medications

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# Standard Operating Procedures for

# Concomitant Medications

## PURPOSE

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| This standard operating procedure (SOP) describes the process of concomitant medication evaluation and review at screening, baseline, and follow-up of participants in the endTB Clinical Trials. Along with the study drugs, study participants may take prescription and over-the-counter drugs or supplements. This information must be collected and documented through the whole period of participation in the study in order to ensure participants’ safety and to prevent potential drug-drug interaction with the study drugs. |

## SCOPE

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| This SOP applies to all study staff members who will be directly involved in concomitant medication evaluation, review, and documentation.  |

## RESPONSIBLE FUNCTIONS

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| **Function** | **Activities** |
| **Site Principal Investigator (site-PI)** | * Supports the delegated site clinician in ensuring that the concomitant medication review is performed according to the study protocol.
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| **Delegated site clinical investigator/ Trial nurse/ Site Pharmacist/Site Study Coordinator** | * Continuously checks concomitant medications against contraindicated concomitant medications listed in this SOP.
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## DEFINITIONS and ABBREVIATIONS

**Adverse Event:** Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

**Concomitant Medications (Con-Med):** Medications taken by a clinical research participant in addition to the study/investigational treatment. Concomitant medications include any prescribed or over-the-counter medications, folk and herbal treatments, vitamin supplements, and illicit drugs or agents acquired on the street to alter body or mind function.

Certain medications are disallowed among participants in the endTB trials: some are disallowed for all study participants from the time of randomization; some require a longer wash-out period before some or all study treatments may be initiated; some are disallowed only for participants receiving specific study drugs; some are noted for QT-interval prolonging effects. The list of drugs is presented in the Appendix. An electronic Concomitant Medication review worksheet, which is equivalent to the list in the Appendix, is also available for consultation.

**International Nonproprietary Name (INN):** The official non-proprietary, generic name given to a pharmaceutical substance by the World Health Organization.

## PROCEDURE

### Preparation

* **Site Principal Investigator (Site PI) and delegated clinicians and pharmacist(s)** must review the list in the Appendix thoroughly to be fully aware of the potential drug-drug interactions and additive toxicities with the study drugs.
* **Site Coordinator and/or delegated personnel** should ensure that the Appendix, and the electronic Concomitant Medication review worksheet, are easily available at the site.
* **Site PI and delegated clinicians and pharmacist(s)** must report in the Concomitant Medication CRF (Form 13) any Con-Med taken by a study participant, whether or not the medication appears in the appendix/Concomitant Medication review worksheet.

### Concomitant Medicine Evaluation

At the screening visit, the **Site PI or delegated clinical investigator** should follow the evaluation procedures as below:

1. Refer to **SOP-010-CT** ***Medical History*** to obtain information about prior and current medications that the participant has recently taken.
2. Ask the participant to list all drugs which s/he is currently taking, or s/he has taken during the last 30 days. For every drug, collect all information listed in the Concomitant Medication CRF. Since participants often do not remember their Con-Med names and doses, it might be helpful to ask participants to bring their pill bottles or package to the study visit for evaluation and review by the doctor.
3. Identify, among all reported Con-Meds, if any is present in the list in the Appendix. If a Con-Med is present in the list, determine:
	* If the participant exposed to this Con-Med at screening can be randomized (second column of the Appendix [Column B]). There are four possible situations:
		+ The participant can be randomized without changes to the Con-Med (answer “Yes” in column B).
		+ The participant can only be randomized if the Con-Med is discontinued, and a sufficient wash-out period is observed between the interruption of the Con-Med and randomization (answer “Yes, after X days of wash-out” in column B). If, in the doctor’s opinion, a Con-Med cannot be stopped or replaced by an allowed, alternative drug with similar efficacy or tolerability, the participant is considered ineligible for randomization.
		+ The participant can only be randomized if it is possible to replace the Con-Med after randomization (answer “Yes, with X days of post-randomization wash-out of all anti-tuberculosis treatment if participant is randomized to a Bdq arm” in column B). This situation is restricted to HIV-positive participants on treatment with antiretrovirals which have interactions with Bedaquiline. Those antiretrovirals will have to be replaced with an alternative antiretroviral only if the participant is randomized to a Bedaquiline-containing experimental treatment arm or requires Bedaquiline in the control arm. Priority should always be given to the participant’s medical condition and well-being. If in the doctor’s opinion, and in consultation with the HIV referral doctor or the Clinical Advisory Committee (CAC), the antiretroviral Con-Med cannot be replaced by an alternative, allowed drug with similar efficacy or tolerability, the participant is considered ineligible for randomization. If the antiretroviral Con-Med can be replaced, the participant is eligible for randomization. After randomization, the antiretroviral treatment will be changed in case of randomization to a Bedaquiline-containing experimental treatment arm or if the participant requires Bedaquiline in the control arm, as follows: 1) If the participant is receiving any protease inhibitor (atazanavir, darunavir, lopinavir, etc.) and has not started Bedaquiline before randomization, or has started Bedaquiline before randomization but has not yet completed a Bedaquiline load, the full anti-tuberculosis treatment, including Bedaquiline, will be started after a wash-out period following randomization as explained in column B; if the participant has already completed a Bedaquiline load and is receiving intermittent Bedaquiline when they are randomized to a Bedaquiline-containing arm, then post-randomization washout is not necessary; 2) if the participant is receiving efavirenz and has not started Bedaquiline before randomization, the full anti-tuberculosis treatment, including Bedaquiline, will be started after a wash-out period following randomization as explained in column B; if the participant is receiving Bedaquiline (daily or intermittently) that they have started before randomization, then post-randomization washout is not necessary.
		+ The participant is not eligible for randomization (answer “No, the participant is not eligible” in column B).
	* If the Con-Med prolongs the QT interval (fourth column of the Appendix [column D]), consider stopping or replacing the drug. If this is not possible, consider increasing the frequency of ECG monitoring during treatment. Continued exposure to a drug in column D is NOT a reason for exclusion unless indicated by column B or C.

### Concomitant Medicine Review

At the baseline visit, the **Site PI or delegated clinical investigator** should follow the evaluation procedures as below:

1. Ask participant if there has been any change to participant’s Con-Meds since screening.
2. Identify, among all reported Con-Meds that have changed since screening, if any is listed in the Appendix. If the Con-Med is listed, proceed as explained above for the Concomitant Medicine Evaluation at screening.

At all follow-up visits, the **Site PI or delegated clinical investigator** should follow the evaluation procedures as below:

1. Ask participant if there has been any change to participant’s Con-Meds since the last visit.
2. If the participant has been exposed to any new Con-Med, and s/he is still taking the study treatment or has stopped study treatment less than 30 days before, determine if the Con-Med is in the list in the Appendix. If the Con-Med is present in the list, determine:
	* If the Con-Med is allowed (third column [C] of the Appendix). There are two possible situations:
		+ No change to the Con-Med is necessary (answer “Allowed” in column C).
		+ The Con-Med is disallowed if the participant is receiving a specific study drug or drugs (answer “Disallowed if receiving X” in column C). If the participant is not taking the named study drug(s), no change to Con-Med is necessary. If the participant is taking the named study drug(s), then the Con-Med is disallowed, and the following procedure should be followed:
			- **Site PI** must be informed and consulted; **Site** **Study Coordinator** should also be informed to file a protocol deviation.
			- Consider stopping or replacing the Con-Med when feasible. If needed, send a query to the CAC for guidance (refer to **SOP SP-024-CT** *Modus Operandi* and *Communication with Clinical Advisory Committee*).
	* If the Con-Med prolongs the QT interval (fourth column [D] of the Appendix): consider stopping or replacing the Con-Med as soon as possible. If this is not possible, consider increasing the frequency of ECG monitoring during treatment. Seek advice from the cardiologist on site and/or the CAC if needed.
3. At the start any Con-Med after randomization, the list in the Appendix should be consulted to avoid disallowed medications. Similarly, the list should be consulted when any new study drug (s) is re-introduced or started: disallowed medications should be stopped before the new study drug (s) is started, observing a wash-out period if needed. Specialists and/or the CAC should be consulted to find alternatives for disallowed medications.

### Concomitant Medicine Reporting

The **Site PI or delegated clinical investigator** must record in the required documents, including the Concomitant Medication CRF (Form 13), information about the participant’s Con-Med(s), whether or not the Con-Med(s) appear in the appendix/worksheet.

### Concomitant Medications and Anti-Tuberculosis Drugs Reporting

In general, the use of any anti-tuberculosis drug for indications other than tuberculosis treatment (i.e. using a carbapenem for a blood stream infection, or clofazimine for leprosy) should be avoided, if possible. However, if there is no alternative treatment, anti-tuberculosis drugs that are not disallowed in the Appendix can be used. The treatment duration with such drugs should be reduced to the minimum.

## REFERENCES

The list of QT-prolonging drugs has been compiled consulting CredibleMeds (<https://www.crediblemeds.org>). All drugs with known, possible, or conditional risk for torsades de pointes were included. The list has been updated to reflect the revision of February 21, 2023.

## SUPPORTING DOCUMENTS

* SOP SP-010-CT Medical History (endTB Site Study Documents).
* SOP SP-024-CT *Modus Operandi* and Communication with Clinical Advisory Committee (endTB Site Study Documents).

## APPENDIX

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| **Number** | **Title** |
| A1 | SP-019-CT\_A1-List of disallowed drugs and drugs that prolong the QT interval. |