Frequently asked questions about the use of cohort event monitoring (CEM) for active pharmacovigilance in TB treatment

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These notes are to be read alongside the main documents dealing with pharmacovigilance and cohort event monitoring CEM produced by the World Health Organization (WHO) and its partners (see references under Further Reading at the end of these FAQs)

What is pharmacovigilance?
Pharmacovigilance (abbreviated here as PV) is defined by the World Health Organization (WHO) as the “science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem”. It is a fundamental activity to inform the management of patient safety measures in health care. PV is a public health surveillance activity. It is another facet of programme monitoring, not too different from the way many countries operate routine surveillance of TB drug resistance based on diagnostic testing.

Are there different approaches to pharmacovigilance for TB drugs?
WHO describes three approaches to PV for tuberculosis (TB) drugs: spontaneous, targeted and active.

- Spontaneous (or voluntary) reporting means that no active measures are taken to look for adverse effects. Reporting to the national authorities responsible for patient safety is entirely dependent on the initiative and motivation of the reporters, usually health care professionals and sometimes the patients. This is the most widespread form of PV globally, and in some countries it is mandated by law.

- Targeted reporting is a variant of spontaneous reporting. It focuses on adverse drug reactions in a well-defined group of patients on treatment and health professionals in charge of the patients are sensitized to report specific safety concerns. This focused approach has the same objectives and uses the same flow of information as for spontaneous reporting. The reporting requires no screening to look for the particular syndromes.

- Active pharmacovigilance means that measures are taken proactively to detect safety concerns. This is achieved by the active monitoring at start, during and at times after treatment. The events may be detected by screening patient records, direct questioning of the patients and through laboratory testing at predefined intervals.
How does active pharmacovigilance differ from spontaneous (or voluntary) pharmacovigilance?

Spontaneous PV is a form of “passive” surveillance. Its effectiveness depends to a large degree on the patient volunteering this information given that individuals have different thresholds to approach formal health-care and to report symptoms; on health-care workers’ competence to recognise an adverse event or to appreciate its importance; and the health-care workers’ motivation to report it to the authorities. One of the key disadvantages of spontaneous reporting is that it does not allow an estimation of the occurrence rates of events. In active PV, besides the spontaneously-reported reactions, adverse events are also elicited as part of a patient monitoring protocol comprising of a set of questions and oftentimes an array of laboratory/clinical tests at defined periods of time, before, during and after treatment. The records from active PV thus make it possible to determine the exact number of patients monitored and the extent of exposure to a drug; they also enumerate the events related to an exposure, in a similar way to a longitudinal epidemiological study.

What is cohort event monitoring?

Cohort event monitoring (CEM) is one of the standard methods of active PV and which has been best defined. It is used to monitor adverse events in patients who receive a particular medication or treatment regimen and to assess causality. A defined cohort (group) of patients is followed up prospectively and all adverse events occurring during treatment and for a given time after its end are registered. Adverse events monitored in CEM do not necessarily have a causal relationship with the treatment, in contrast to established adverse drug reactions, and a causality assessment will thus be required. CEM has been used in both high and low income settings (see articles cited under Further reading). Beyond its role as part of risk management, CEM can provide useful insights into patterns of utilization and the adoption of a new drug in clinical practice (e.g. acceptability by clinicians and patients). Given the importance at this early stage of observing the largest possible number of exposures to new drugs in a systematic and comparable manner across countries, the adoption of forms of PV other than CEM - such as targeted PV or reporting from sentinel sites - is not being advised and all patients treated with the new drugs should be included in CEM.

Why is WHO recommending CEM when bedaquiline or delamanid are used?

WHO recommended the use of these two drugs in TB patients with multidrug-resistant TB (MDR-TB) upon condition of active PV. This recommendation was supported by the independent experts who reviewed the information available on safety of bedaquiline and delamanid in the Guideline Development Group meetings held in 2013 and 2014 respectively. Both of these medicines are still relatively new and only a limited number of patients have been treated with them. In both cases the decision to grant conditional marketing approval by stringent drug regulatory authorities prior to the completion of Phase 3 trials took into account the serious nature of MDR-TB and the unsatisfactory outcomes obtained when regimens composed solely of older second-line drugs are used. All reasonable measures are thus needed to ensure that patient safety is monitored alongside the effectiveness of the treatment.
In this situation, spontaneous reporting is not expected to represent an appropriate level of care and active PV techniques, such as CEM, are considered necessary to improve the early and systematic detection of harms. It is also important to collect safety data accurately and undertake causality assessment carefully in order to ensure that all adverse events are properly investigated and that no premature conclusions are drawn regarding the attribution of cause. Causality assessment is thus very important.

**Is CEM the same as a clinical trial? Will it replace the Phase 3 studies of new drugs?**
No. CEM remains an observational type of study of a cohort (group) of patients who are taking a particular medication or regimen. It is intended to be conducted under programmatic conditions, without any randomization of study subjects to intervention and to control / comparison arms. Operational research on other aspects of care can be built alongside CEM, such as a comparator cohort of patients receiving standard care to be monitored concurrently. Phase 3 trials for bedaquiline and delamanid, which will randomize patients to control and intervention arms, will still be needed to look more closely at the efficacy and toxicity of these drugs.

**Are there practical examples of CEM for TB?**
CEM and active PV are relatively new concepts within the span of monitoring activities of national TB programmes. There is more experience in resource-limited settings with CEM in treatment programmes for other diseases, such as malaria and HIV (refer to two projects under Further reading). A number of countries in Africa and elsewhere have recently introduced active PV within cohorts of patients treated with shorter-regimens for MDR-TB.

**Am I expected to have CEM even for old TB drugs?**
CEM is currently being recommended by WHO when TB patients are placed on new drugs or on treatment regimens that differ substantially from those in general use. Given that these situations would always require the use of companion, legacy TB drugs, CEM will allow the monitoring of adverse effects to the older drugs in the regimen. Programmes can however opt to use CEM more extensively and there are recent examples where CEM has been successfully used for MDR-TB patients on standard regimens without new drugs, or MDR-TB patients who have repurposed drugs (eg, linezolid) included in their combination therapy. Other approaches to PV (e.g. targeted reporting) can be adopted for routine use in TB treatment programmes.

**Is it true that for CEM I need to follow up least 10,000 patients on treatment?**
Apart from detecting known, frequent adverse reactions, CEM should also provide information about rare and as-yet unrecognised adverse effects and drug-drug interactions. The 10,000 figure helps illustrate the point that when an adverse drug reaction occurs as rarely as once in 2,000-3,000 exposures, only a handful of events may occur even when large numbers of cases are observed. With a few exceptions, it is not expected that such numbers accrue in any single country and pooling of data across countries would be needed for a comprehensive analysis of risk. Sample-size calculation, as is the practice in epidemiological studies, is not being
recommended for CEM. It is important that health professionals are trained to keep close scrutiny on patients within an observational study setting to avoid missing rare events.

So will WHO change its policy only after at least 10,000 patients have been put on treatment?
Not necessarily. While detection of rare events is important, the overall aim of applying CEM when using these drugs is to develop a safety profile based on a larger number of observations than now. The policy may actually need to be changed when much less than 10,000 patients receive the drug if unexpected safety concerns emerge.

I am a programme manager and I expect to be treating between 10-50 patients on bedaquiline or delamanid in the coming years. Do I still need to monitor adverse effects as intensely as in CEM?
Yes. CEM is important when patients are treated with a medicine for which the drug safety profile is as yet incomplete. This does not depend on the number of patients enrolled. The best described method to operationalise active PV is CEM. Monitoring needs to be closely associated with early action to prevent and manage any serious consequences to the individual patient. A national programme should also strive to capture data in the private sector and public-private partnerships.

When using bedaquiline should I only focus on signs of cardiotoxicity?
No. CEM is intended to pick up not only the known reactions associated with a drug but also any unexpected effect of treatment (some of these may actually be beneficial to the patient). It is expected that the adverse reactions which are already known to be associated with a new drug or regimen will occur among the patients treated and these need to be detected early. However, for drugs like bedaquiline and delamanid, which have only been administered to a relatively limited number of patients, a broader perspective needs to be applied.

If a patient gets a reaction how can I tell which drug is causing it (all MDR-TB patients are having combination TB chemotherapy)?
The most common adverse effects to be expected of a medicine are often those which have already been reported in patients exposed to it and which result from interactions with concomitant medication. Some of them can be plausibly explained by the drug’s pharmacodynamics / pharmacokinetics. However, with drugs that have not yet undergone Phase 3 trials, the number of patients exposed to treatment is relatively low and important adverse reactions may not yet be well characterized. Continued vigilance for unknown or unrecognised untoward effects is important. When multiple drugs are used an important method which is used to assess causality is dechallenge +/- rechallenge (withdrawal +/- reintroduction), with observation of the clinical effects. One of the strengths of CEM is that it allows a more systematic approach and closer monitoring of the events in such a situation. At times the attribution of an effect to a particular drug cannot be determined with certainty (e.g. liver toxicity in a patient on rifampicin+isoniazid+pyrazinamide). In the case of new drugs it is crucial that a causality assessment is undertaken and the findings communicated prudently, as incorrect attribution of harms to any of these medicines could lead to irreversible harm to their
reputation and even reflex withdrawal from markets, thus depriving patients of the potential benefits of the drugs.

**Many MDR-TB patients get mild reactions on treatment. Should I just focus on the severe events?**

For CEM, a non-severe event may be the early manifestation of a more consequential process (e.g. a dose-dependent effect). Such events should be captured on the data collection forms. To reduce workload it is usually left optional to the projects to undertake causality assessment in such events.

**How do I know that an event is severe? Is it the same as a “serious” event?**

Severity is a subjective assessment made by the patient and/or the health care professional of the intensity of an event and relates to its impact on the patient’s activities. Severity is often classified on a three-point scale from “mild” through “moderate” to “severe”, commonly on the basis of a clinician’s judgement. Practitioners would however want something less subjective on which to base their classification. There are different scales to classify severity (such as **DAIDS**¹, **CTCAE**², and **ANRS**³). Any of these can be used; it is important to note that none of them have been developed specifically for TB medicines and some adaptations may be needed. Seriousness is another dimension of an event and differs from severity; it relates more to the consequences of an event. A serious event is one which either leads to death or to a life-threatening experience; hospitalization or prolongation of hospitalization; persistent significant disability; or congenital anomaly. An event may be severe but not serious, or vice versa, or both: most commonly they are neither.

**Do I classify death as a severe event?**

Death is considered an outcome rather than an event (see the sample [reporting forms]⁴). Death may be a sequel to a severe event. It may also be sudden and not preceded by any particular event. An event which leads to death is considered serious.

**What do I do if a patient on a new drug dies or sustains a serious disability? Should I stop the drug for all patients?**

MDR-TB patients on treatment are known to have a higher risk of dying than other TB patients. Drugs like bedaquiline and delamanid may be used in a subset of MDR-TB patients who are at an even higher risk of dying. Careful examination of serious events in patients on this treatment must thus be done to ascertain the circumstances leading to death or disability. If the episode cannot be explained by what is known about the pharmacology of the drug the manufacturer should be alerted (Janssen Therapeutics, the manufacturer of bedaquiline, requests programmes to send information within 24 hours of deaths and serious adverse events

1 [rsc.tech-res.com/Document/safetyandpharmacovigilance/Table_for_Grading_Severity_of_Adult_Pediatric_Adverse_Events.pdf](http://rsc.tech-res.com/Document/safetyandpharmacovigilance/Table_for_Grading_Severity_of_Adult_Pediatric_Adverse_Events.pdf)
2 [evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf](http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf)
4 [www.who.int/entity/tb/challenges/sample_data_collection_forms_for_cem_to_antibb_drugs_27march.pdf](http://www.who.int/entity/tb/challenges/sample_data_collection_forms_for_cem_to_antibb_drugs_27march.pdf)
occurring in patients on this drug). It is important that any unexpected reaction with a serious or fatal outcome due to a drug is rapidly identified and investigated. Equally important is that no hasty conclusions are drawn on causality within a context of very limited treatment options for a serious condition and where the confidence of patients and health-care professionals in a potentially life-saving drug could be irreparably damaged. Programmes should prepare what to do in the event of a serious episode, including how to communicate it factually and constructively. The WHO Collaborating Centre in Uppsala, Sweden, has produced a comprehensive publication based on experience from real-life situations which provides helpful instruction on how best to act under such circumstances (see Further reading below).

**How much does it cost to implement CEM? Can I put this in the Concept Note to be submitted to the Global Fund?**

The main costs associated with CEM relate to initial preparation for the training of staff, information and education of patients, the production of data collection materials, and the creation or adaptation of a database in which to consolidate the data. Once the system is in place, much of the running costs will represent marginal expenses of an additional surveillance activity albeit the labour costs may be substantial. The total amount will vary between countries and depends on the number of centres involved. Programmes should obtain technical advice to cost their specific needs more accurately (the costs can also be calculated using the WHO Tool for Planning and Budgeting for TB control activities; programmes should set aside at least USD50,000 to provide for the initial preparations). The costs for CEM may be included in a request for funding to the Global Fund under the New Funding Model.

**Do I need to have CEM up and running before I order or enroll patients on bedaquiline or delamanid?**

Fully functional CEM is not required up front at the time of ordering the drugs or starting patients on treatment. However, certain key elements need to be in place so that the essential safety data are collected for all patients the moment that they are started on regimens containing a new drug: a broad agreement between the national TB programme and the national PV centre on the process to implement CEM for TB drugs; preparations for the collection of data (e.g. forms); and staff properly trained to collect the data. This will ensure that the programme is prepared to collect the patient data from the very start of CEM (both the Initiation and Review phases; see forms). Local capacity for CEM needs to be built within the TB and/or PV centre over the following months. Table 1 shows how the 9 key steps for the establishment of CEM could be addressed ahead of the start of patient recruitment, building upon the strengths of the monitoring framework that NTPs are accustomed to when following up their patients. There is a substantial amount of additional work that is required to mount and maintain CEM but the TB monitoring approach is a clear advantage that TB programmes have over other disease programmes when implementing CEM.

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5 [www.who-umc.org/](http://www.who-umc.org/)
7 [www.who.int/entity/tb/challenges/sample_data_collection_forms_for_cem_to_antitb_drugs_27march.pdf](http://www.who.int/entity/tb/challenges/sample_data_collection_forms_for_cem_to_antitb_drugs_27march.pdf)
Can I monitor the safety of patients on new drugs using something “lighter” than CEM?

This is not recommended. While it is important that additional demands for data from both the programme and the patients are minimised, the essential data elements need to be collected in accordance with the time schedule established by the programme. Without this it will be difficult if not impossible to undertake meaningful signal detection and causality assessment both locally as well as at supranational level.

Do you need ethics clearance to undertake CEM?

The same local requirements for ethics approval that govern routine public health surveillance activities should apply. Attention must be paid to the confidentiality of patient information.

Is patient consent required?

WHO recommends, as one of the conditions for use of the new drugs, that patients provide informed consent and guidance on what this should include is provided in the Annexes to the Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. This covers also the areas of confidentiality and sharing of information. It makes it clear that given the limited experience on these drugs, programmes are collecting patient information to improve knowledge on them, while making a commitment to keep all medical information confidential and to make all information anonymous before it is shared or analysed beyond the clinical staff looking after the patient.

Where do I get the CEM “questionnaire”?

Rather than creating new data collection forms it would be best to insert the essential data elements into the existing patient TB treatment card so that the CEM data are collected as a matter of routine, alongside other patient details at initial registration and during the follow up visits. For instance the treatment card developed by the UNION for the multicentre study of shorter regimens is one example of how this could be done. Ideally data should be collected electronically at source, via mobile devices or desktop. Otherwise, sample data collection forms (“questionnaires”), which can be freely adapted for use at country level, are accessible on the WHO website.

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8 www.who.int/tb/publications/pmdt_companionhandbook/en/
9 www.who.int/entity/tb/challenges/sample_data_collection_forms_for_cem_to_antitb_drugs.pdf
Table 1. Implementation of the “9 steps” for CEM in TB programmes

<table>
<thead>
<tr>
<th>STEPS</th>
<th>Needed ahead of patient recruitment?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Establishment of CEM committee &amp; secretariat</td>
<td>Yes; this can be a group such as the MDR-TB expert committee (or Consilium) with appropriate representation from the PV centre</td>
</tr>
<tr>
<td>Management and supervision</td>
<td>Yes; the main responsibilities need to be assigned to the main actors</td>
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<tr>
<td>Preparation of CEM protocol, including plan for data analysis and communication</td>
<td>In part; this can be a supplement to the national TB guidelines and the full detail can be worked into it at a later stage</td>
</tr>
<tr>
<td>Design and production of forms for data collection</td>
<td>Yes; the essential data elements for CEM should ideally be worked into the standard TB treatment card for second-line treatment. Otherwise, if separate data collection forms will be used, templates for both the initiation and review questionnaires are available on the WHO7 website (see also FAQs)</td>
</tr>
<tr>
<td>Submission for ethics approval</td>
<td>Only if required by local authorities. Patient informed consent for the use of the drugs also includes acceptance for confidential use of information</td>
</tr>
<tr>
<td>Staff training</td>
<td>Yes; this should be done alongside the training of health care workers on how to use the new drug. It is best to have a training module which combines adverse drug reaction reporting as part of the indicators for MDR-TB monitoring</td>
</tr>
<tr>
<td>Collection of data</td>
<td>Yes; the collection of data (be it on the adapted treatment card or on special forms) would be done during the scheduled patient visits for the Initiation (baseline) and Review of treatment. For causality assessment, more data may be needed from a patient or physician and this should preferably be done as soon as possible after the event</td>
</tr>
<tr>
<td>Electronic database for MDR-TB patients on treatment, for consolidation of PV data</td>
<td>Not essential initially; can be developed in the months following the first enrolments although delay in data entry should be avoided.</td>
</tr>
<tr>
<td>Relationship/causality assessment</td>
<td>This will usually require specialist skills and is only expected to be</td>
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</table>
I have read your handbooks and realised that I do not know how to code adverse events, or to do signal detection and causality assessment. Is there a training course that I can follow on this?

These tasks require specialist input and such expertise may be housed in the PV centre of your country. It is therefore important that liaison with the national centre responsible for drug safety is established early so that this component of CEM is addressed.

They tell me that there is no centre doing PV in my country. Who will help me do this?

If you are considering to start CEM and there is no functional national PV centre please contact WHO for advice on how to access expertise or training on active PV and CEM.

Where do I send the data collection forms after I complete them? And how often?

The data - or forms if CEM data collection is organised using paper “questionnaires” - are best transferred to the place where their contents will be databased, either at the facilities, within the TB programme or at the national PV centre. An arrangement will need to be found on how to check the contents of the forms for completeness and errors, making corrections, copying/scanning of contents, electronic registration, and anonymization and safe storage of the paper forms for a number of years before destruction (standard operating procedures - SOP - are encouraged). The data or forms need to be consolidated as frequently as the analysis for causality is done; in the case of a serious adverse event this should be done rapidly after. Local legal requirements may govern the reporting and assessment of events. Local capacity needs to be built to ensure that this process runs effectively.

Will WHO be setting up a registry of patients on new drugs?

In order to revise its interim guidance on bedaquiline and delamanid in the coming years, WHO will need to assess the evidence drawn from global experience with these medicines. For this a pooled analysis of data from several countries is envisaged. The method by which this supranational analysis will be done is currently being discussed and will be communicated to the programmes later in 2015. Meanwhile, the manufacturers of the drugs may also be organising their own systems to collect safety data (e.g. Janssen Therapeutics has set up a registry for patients on bedaquiline in the United States).

Our pharmacovigilance centre tells me that we need to send all the questionnaires to somewhere in Sweden. Can you give me the email or fax of the person to send it to?

The national PV centres need to continue to report adverse drug reactions to the WHO Collaborating Centre in Uppsala in Sweden within the framework of the Programme for

10 www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/
International Drug Monitoring\textsuperscript{11}. This also includes adverse reactions attributed to the new drugs. However, there will be a separate arrangement for the supranational sharing of country CEM data. This is being discussed at this point in time (April 2015). It is important that countries consolidate these data in as standardised a manner as possible from the beginning so as to facilitate the comparability of episodes when analyses are performed on data pooled from various units located in different parts of the world.

**If WHO is not collecting the individual patient data then why do we need to collect them?**

CEM is primarily meant to help the national programmes undertake appropriate surveillance for adverse events among *their own patients* when they are treated with new drugs such as bedaquiline and delamanid. The methods described for establishing CEM are meant to ensure that there is a sound framework for a systematic, regular monitoring of adverse events (information elicited through questions to the patient and a series of laboratory and clinical examinations) to be observed at defined time-points before, during and after treatment. The collection of standardized data for this purpose will thus be important and it is crucial that this is organized properly early on. The recommended standards for the collection of essential data elements have been compiled into a “data dictionary” by WHO and its partners (see Annex 1a of the Report of the [Inter-regional workshop on pharmacovigilance for new drugs and novel regimens for the treatment of drug-resistant TB](http://www.who.int/tb/challenges/meeting_report_pv_workshop_hanoi_2014.pdf)\textsuperscript{12} held in November 2014 in Viet Nam under Further reading).

WHO anticipates that the policies on the use of bedaquiline and delamanid will be updated within a few years’ time. An analysis of multi-country data will be needed to inform this process. Using data collected across different national cohorts will bring the number of cases observed closer to the total needed for a rare event to have a reasonable likelihood of being detected. It will also diversify the profile of the population exposed in terms of key demographic and clinical characteristics, such as age-group, comorbidity, ethnicity, and the background regimen to which the new drug is added. The way in which this pooled analysis will be organised is being discussed at this point in time - including the competence and experience of providers to undertake this work; at what frequency the data will be requested; and issues of data validity and ownership. Details on the mechanism will be communicated by WHO Global TB Programme later in 2015.

**Why do I need the data dictionary if I am only going to analyze the data in my country?**

Besides the sharing of data for pooled analysis across different countries the data need to serve the purposes of the national programmes. For this purpose it is also important that the data are collected in a systematic manner which permits comparability of events between different patients and over time. Many programmes will not be familiar with some of the data which are needed and the dictionary will help them understand these elements. Ideally these data are

\textsuperscript{11} www.who-umc.org/

\textsuperscript{12} www.who.int/tb/challenges/meeting_report_pv_workshop_hanoi_2014.pdf
integrated within the existing stationery (e.g. TB treatment card) or electronic database used for TB patients, in order to avoid duplication of data collection.

How do I analyze the data? Can you give me the name of consultants who can help me do this?
The analysis of data should best be done by an expert in drug safety: this is usually the duty of the national PV centre. For more advanced analyses the expert input of a specialist in the field of biostatistics may also be necessary. If this expertise is not available in the country you may contact WHO for further advice.\(^\text{13}\)

Is there software to analyse the questionnaire data?
No specific software is currently recommended specifically for the management or analysis of CEM data. Some national TB programmes are either expanding their existing electronic database for TB patients to accommodate the additional variables needed for CEM; others are creating special databases solely for CEM. When creating new systems it is important to ensure good collaboration between the TB and PV authorities and to adhere to the best practices recommended by WHO (see reference below). The analysis of the data requires a systematic approach: line-listing and eye balling of all episodes is a first step (this can be done with any spreadsheet package). Any suspected associations may be tested for statistical significance using univariate techniques or multivariable regression; a number of software packages can do this (e.g. R, STATA, SAS).

How do I create the drug safety profile?
An outline of a drug safety profile is provided in the Report of the Inter-regional workshop on pharmacovigilance for new drugs and novel regimens for the treatment of drug-resistant TB\(^\text{14}\) held in November 2014 in Viet Nam (see under Further reading). It is not expected that a full “safety vs. benefit” profile of a medicine can be based on the experience of any one single country and therefore the more data that are available the better the reliability of the profile. As is the case for the supranational collection and analysis of data, the elaboration of the drug safety profile is a subject of current discussion and more details will be provided by WHO about this later in 2015.

What are the indicators that I need to report to WHO for patients on CEM?
Five basic indicators are proposed (Table 2) and they are explained in the Report of the Inter-regional workshop on pharmacovigilance for new drugs and novel regimens for the treatment of drug-resistant TB\(^\text{15}\) (see under Further reading below). For a number of them stratifications are recommended, such as by organ class or by severity. Out of the five indicators, the first and the third are considered essential to have in CEM. As for all other aspects of CEM, the indicators are primarily intended to help programmes assess the safety of the new medication and not solely as outputs to report to WHO. In addition to the indicators it is also important that the PV centre keeps sending individual case safety reports to the WHO Collaborating Centre in

\(^{13}\) www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/


\(^{15}\) www.who.int/tb/challenges/meeting_report_pv_workshop_hanoi_2014.pdf
for patients included in CEM who develop adverse drug reactions, the same as they would do for spontaneous reports (preferably through VigiFlow), within WHO’s established Programme for International Drug Monitoring, which is subscribed to by over 100 countries as full members.

Table 2. Summary indicators for CEM in TB programmes

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target RR-/MDR-TB patients included in cohort event monitoring</td>
<td>Numerator: Number of TB cases started on target treatment included in CEM during the period of assessment. Denominator: Number of TB cases started on target treatment during the period of assessment and who were eligible for CEM.</td>
</tr>
<tr>
<td>Time to stopping target drug</td>
<td>The difference in days between the date of start of treatment with a target drug and the date of the stopping the target drug. The calculation is done for each member of the cohort</td>
</tr>
<tr>
<td>RR-/MDR-TB patients included in CEM with any serious adverse event</td>
<td>Numerator: Number of TB cases included in CEM during the period of assessment with one or more serious adverse events. Denominator: Number of TB cases included in CEM during the period of assessment.</td>
</tr>
<tr>
<td>Frequency of adverse drug reactions associated with the target treatment</td>
<td>Numerator: Number of adverse drug reactions attributed to target treatment among patients on CEM. Denominator: Number of TB cases included in CEM during the period of assessment.</td>
</tr>
<tr>
<td>Time to development of adverse drug reactions associated with the target treatment</td>
<td>The difference in days between the date of start of the target treatment and the date of the first detected onset of the adverse drug reaction attributed to it</td>
</tr>
</tbody>
</table>

Further reading


16 www.who-umc.org/


