Frequently asked questions about active TB drug-safety monitoring and management (aDSM)

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The Global TB Programme of World Health Organization (WHO/GTB) issued interim policy on the use of two new medicines - bedaquiline and delamanid - since 2013. In May 2016, WHO conditionally recommended a shorter MDR-TB regimen for selected patients. One of the conditions set for the implementation of these policies is active pharmacovigilance. These “frequently asked questions” (FAQs) summarize current WHO advice on the implementation of pharmacovigilance and management of drug safety specific to the context of TB programmes. The FAQs are to be read alongside the main documents dealing with active drug-safety monitoring and management (aDSM) produced by WHO and its partners (see Further Reading at the end of these FAQs for the respective documents).

What is pharmacovigilance?
Pharmacovigilance is defined by WHO as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem”. WHO identifies two main approaches to pharmacovigilance: spontaneous and active.

- **Spontaneous** (or voluntary) reporting means that no active measures are taken to look for adverse reactions. 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 pharmacovigilance globally, and in some countries it is mandated by law. One of the key disadvantages of spontaneous reporting is that it does not allow an estimation of the occurrence rates of events.

- **Active** pharmacovigilance means that measures are taken proactively to detect safety concerns. This is achieved by active monitoring at start of, during and at times after the end of treatment. The events may be detected by screening patient records, direct questioning of the patients and through laboratory testing at predefined intervals.

What is active TB drug-safety monitoring and management (aDSM)?
aDSM defines the active and systematic clinical and laboratory assessment of patients on treatment for extensively drug-resistant TB (XDR-TB), or with new TB medicines or novel regimens for multidrug-resistant TB (MDR-TB) to detect, manage and report suspected or confirmed drug toxicities. The recording and reporting activities of aDSM primarily target the serious adverse events (SAEs) as a priority requirement. MDR-TB treatment sites may also monitor other AEs which are of clinical significance or of special interest to the programme, as part of comprehensive aDSM.

aDSM is used to monitor and manage adverse events in patients who receive a particular medication or treatment regimen and to assess causality. It applies the principles of active pharmacovigilance to the specific needs and context of national TB programmes and is embedded within the patient monitoring function (e.g. cohort monitoring) of TB programmes. The management of patient safety is an inherent part of aDSM, inseparable from its monitoring component.
In aDSM, besides the spontaneously reported reactions, adverse events are also elicited as part of a patient monitoring plan 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 TB drug-safety monitoring thus make it possible to determine the exact number of patients monitored and the extent of exposure to a medicine; they also enumerate the events related to an exposure, in a similar way to a longitudinal epidemiological study.

The WHO Global TB Programme (WHO/GTB) therefore convened key technical and funding agencies to a meeting in Geneva, Switzerland on 28-29 July 2015 to discuss essential requirements for the implementation of active pharmacovigilance and proper management of adverse events (AEs) when introducing new anti-TB medicines or novel MDR-TB regimens. The document Framework for implementation of active tuberculosis drug-safety monitoring and management (aDSM) reflects the consensus achieved during this meeting and in subsequent discussions also involving NTP managers of selected countries and the WHO Essential Medicines and Health Products Department(1).

**Why is WHO recommending aDSM?**

WHO recommended the use of bedaquiline, delamanid and the shorter MDR-TB regimen upon condition of active drug-safety monitoring(2),(3),(4),(5),(6). 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. Likewise, the 2016 recommendation for a shorter MDR-TB regimen preceded the results of a randomised controlled trial (RCT) of its use. 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 more active approaches, such as aDSM, are considered necessary to improve the early and systematic detection and proper management 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.

**When does aDSM apply?**

aDSM applies to the following groups:
- TB patients treated with new medicines, such as bedaquiline or delamanid;
- TB patients enrolled on treatment with novel regimens, such as the shorter MDR-TB treatment regimen;
- All XDR-TB patients on second-line treatment (as these regimens often include multiple repurposed medicines).

Once these priority groups of patients are covered, aDSM can be extended to other patients on treatment with longer MDR-TB regimens.

**Do all treatment centres need to apply the same package of aDSM?**

There are three levels of monitoring in aDSM:
1. **Core package:** requiring monitoring for and reporting of all SAEs
2. Intermediate package: includes SAEs as well as AEs of special interest
3. Advanced package: includes all AEs of clinical significance

All centres treating eligible patients with new anti-TB medicines or novel MDR/XDR-TB regimens require the Core package. These treatment centres should, as a minimum, also be taking part in spontaneous reporting of ADRs as required by local regulations. Expansion of aDSM should be implemented in a phased approach.

**Is aDSM the same as a clinical trial? Will it replace the Phase 3 studies of new medicines?**

No. aDSM 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 or comparison arms. Operational research on other aspects of care can be built alongside aDSM, 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, and RCT data for the shorter MDR-TB regimen and other novel treatment, will still be needed to look more closely at the efficacy and toxicity of these medicines.

**Are there practical examples of aDSM for TB?**

aDSM is a relatively new concept within the span of monitoring activities of national TB programmes. There is more experience in resource-limited settings with aDSM in treatment programmes for other diseases, such as malaria and HIV. A number of countries in Africa and elsewhere have recently introduced active drug-safety monitoring within cohorts of patients treated with the shorter MDR-TB regimen.

**Are NTPs expected to implement aDSM even for old TB medicines?**

aDSM is currently being recommended by WHO when TB patients are placed on new or repurposed medicines, treatment of XDR-TB, or on novel treatment regimens that differ substantially from those in general use. Programmes can however opt to use aDSM more extensively and there are recent examples where aDSM has been successfully used for MDR-TB patients on standard regimens without new medicines, or MDR-TB patients who have repurposed medicines (e.g. linezolid) included in their combination therapy.

**Is it true that for aDSM there is need to follow up least 10,000 patients on treatment?**

Apart from detecting known, frequent adverse reactions, aDSM should also provide information about rare and as-yet unrecognised adverse reactions 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 aDSM. It is important that health professionals are trained to keep close scrutiny on patients within an observational study setting to avoid missing rare events. Reporting of SAEs by countries to the global aDSM database ([http://www.who.int/tdr/research/tb_hiv/adsm/en/](http://www.who.int/tdr/research/tb_hiv/adsm/en/)) established in 2016 will increase the likelihood that signals of unknown or poorly documented drug-related harms are elicited by analysing pooled data.
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 aDSM when using new regimens 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 medicine if unexpected safety concerns emerge.

I am a TB programme manager and my programme expects to be treating between 10-50 patients on bedaquiline or delamanid in the coming years. Does my programme still need to monitor adverse reactions as intensely as in aDSM?

Yes. aDSM 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 drug-safety monitoring is aDSM. 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. Similar monitoring is needed for the shorter MDR-TB regimen.

When using bedaquiline should NTP and health care providers only focus on signs of cardiotoxicity?

No. aDSM is intended to pick up not only the known reactions associated with a medicine 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 medicine or regimen will occur among the patients treated and these need to be detected early. However, for medicines 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 medicine is causing it (all MDR-TB patients are having combination TB chemotherapy)?

The most common adverse reactions 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 pharmacodynamics / pharmacokinetics of a medicine. However, with medicines 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. In the case of new medicines 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 medicines.
Many MDR-TB patients get mild reactions on treatment. Should NTP and health care providers just focus on the serious adverse events (SAEs)?

For aDSM, all centres treating eligible patients with new TB medicines or novel MDR-TB regimens require the Core package that requires reporting of all SAEs. However, proper clinical and laboratory management as well as detection and treatment of all adverse drug reactions must be in place. All SAEs detected should be reported to the national authority responsible for pharmacovigilance according to individual country requirements and should be regularly assessed for causality. In addition to the priority requirement to monitor SAE, M/XDR-TB treatment sites may also monitor other AEs which are of clinical significance or of special interest to the programme, as part of comprehensive aDSM. aDSM may also be expanded in a phased approach to eventually cover TB patients on treatment with any second-line medicines.

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

Seriousness is a dimension of an event that differs from severity, relating 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. In contrast 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 may however want something less subjective on which to base their classification. There are different scales to classify severity (such as DAIDS(7), CTCAE(8), and ANRS(9)). 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 thus be needed. An event may be severe but not serious, or vice versa, or both: most commonly they are neither.

Do I classify death as a serious event?

Death is considered an outcome rather than an event. An event which leads to death is considered serious.

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

MDR-TB patients on treatment are known to have a higher risk of dying than other TB patients. Medicines 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 medicine the manufacturer should be alerted. Programmes need to inform manufacturer within 24 hours of deaths and serious adverse events occurring in patients on the new medicine. It is important that any unexpected reaction with a serious or fatal outcome due to a medicine 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 medicine 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 (http://www.who-umc.org/) has produced a comprehensive publication based on experience from real-life situations which provides helpful instruction on how best to act under such circumstances(10).
How much does it cost to implement aDSM? Can NTP or partners put this in the Concept Note to be submitted to the Global Fund?

The main costs associated with aDSM 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 Planning and Budgeting Tool for TB control activities (http://www.who.int/tb/areas-of-work/monitoring-evaluation/financing/planning-tool/en/); programmes should set aside at least USD50,000 to provide for the initial preparations). The costs for aDSM may be included in a request for funding to the Global Fund under the New Funding Model.

Do NTP and health care providers need to have aDSM up and running before they order or enrol patients on bedaquiline or delamanid?

Fully functional aDSM is not required up front at the time of ordering the medicines or starting patients on treatment. However, two 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 medicine: creation of the standard data collection materials (e.g. paper or electronic forms; see sample forms (http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/sample_data_collection_forms_for_adsm_18022016.pdf)); and staff properly trained to collect the data. The NTP needs to assign someone from the start to coordinate the process, ensure that the two minimum elements are in place; and develop a protocol and have it approved. In this work, the person should ideally involve experts from relevant disciplines convened by the NTP to steer aDSM at national level (this could be one function of the MDR committee or consilium). Local capacity for aDSM needs to be built within the TB and/or drug-safety monitoring centre over the following months. Table 1 shows how the 8 key steps for the establishment of aDSM could be addressed in the process of patient recruitment, building upon the strengths of the framework that NTPs are accustomed to when monitoring their patients for treatment response and outcomes. There is a substantial amount of additional work that is required to mount and maintain aDSM but the traditional monitoring approach inherent to TB programmes is a clear advantage over other disease programmes when implementing aDSM.

Can NTP and health care providers monitor the safety of patients on new medicines using something “lighter” than the core package of aDSM?

This is not recommended, since the aDSM Core package is already a minimum requirement for monitoring drug safety in TB programmes. 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 causality assessment as well as signal detection, both locally as well as at global level.

Do NTP and health care providers need ethics clearance to undertake aDSM?

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.
Table 1. Implementation of the 8 steps for aDSM in TB programmes

<table>
<thead>
<tr>
<th>STEPS</th>
<th>Needed ahead of patient recruitment?</th>
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<tbody>
<tr>
<td>Create a national coordinating mechanism for aDSM</td>
<td>The NTP needs to assign someone from the start to coordinate the introduction of aDSM. This should ideally involve experts from relevant disciplines convened by the NTP to steer aDSM at national level (e.g. as one function of the MDR committee)</td>
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<td>Develop a plan for aDSM</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>
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<td>Define management and supervision roles and responsibilities</td>
<td>The main responsibilities need to be assigned to the main actors</td>
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<tr>
<td>Create standard data collection materials</td>
<td>Yes; the essential data elements for aDSM 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 WHO website (see also FAQs)</td>
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<tr>
<td>Train staff on the collection of data</td>
<td>Yes; this should be done alongside the training of health care workers on how to use the new medicine. 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>Define schedules and routes for data collection and reporting</td>
<td>In part; 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>
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<tr>
<td>Consolidate aDSM data electronically</td>
<td>Not essential initially; can be developed in the months following the first enrolments although delay in data entry should be avoided.</td>
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<tr>
<td>Develop capacity for signal detection and causality assessment</td>
<td>This will usually require specialist skills and is only expected to be developed with time within the TB and/or drug-safety monitoring programmes</td>
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Is patient consent required during aDSM implementation?

WHO recommends informed consent as one of the conditions for use of the new medicines 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* (11). This covers also the areas of confidentiality and sharing of information. It makes it clear that given the limited experience on these medicines, 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 aDSM “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 aDSM 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 MDR-TB regimens is one example of how this could be done. Ideally data should be collected electronically at source, via mobile devices or desktop(12). Otherwise, sample data collection forms (“Questionnaires”), which can be freely adapted for use at country level, are accessible on the WHO Global TB Programme website (http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/sample_data_collection_forms_for_adsm_18022016.pdf).

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 drug-safety monitoring 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 aDSM is addressed. Also, in many countries international partners are working in the field of pharmacovigilance and introduction of new medicines. They can provide technical assistance and trainings, per country request.

I was told that there is no centre doing drug-safety monitoring in my country. Who will help me do this?

If you are considering starting aDSM and there is no functional national drug-safety monitoring centre please contact WHO for advice on how to access expertise or training on active drug-safety monitoring and aDSM. You can also collaborate with international partners working in your country in the field of pharmacovigilance and introduction of new medicines (such as Challenge TB Project, MSH/SIAPS, etc.)

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

The data - or forms if aDSM 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 drug-safety monitoring centre. An arrangement will need to be found on how to check the contents of the forms for completeness and errors, make corrections, copy or scan their contents, register them electronically, and store the paper forms safely and confidentially 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. It is highly recommended that countries use an electronic database (either an existing one or a new one) in order to collect and report aDSM data.
Will WHO be setting up a registry of patients on new medicines?

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 involves the use of a global aDSM database, established by WHO/TDR in 2016 (http://www.who.int/tdr/research/tb_hiv/adsm/en/).

Our drug-safety monitoring 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 reporting to the global aDSM database, which is physically located in Luxembourg, follows a specific methodology (http://www.who.int/tdr/research/tb_hiv/adsm/en/). It is important that countries consolidate their aDSM 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. It is highly recommended that countries use electronic database (either existing or developing new one) for collecting, and reporting aDSM data.

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

aDSM is primarily meant to help the national programmes undertake appropriate clinical management and surveillance for adverse events among their own patients when they are treated with novel regimens and new medicines such as bedaquiline and delamanid. The methods described for establishing aDSM 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 (http://www.who.int/tdr/research/tb_hiv/adsm/en/). WHO anticipates that the policies on the use of bedaquiline and delamanid will be updated within a few years as new data are generated. 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 medicine is added.

What is the difference between the drug-safety data collected through aDSM by the NTP and the data to be collected and reported to Janssen in relation to the bedaquiline donation programme?

Safety data of patients receiving bedaquiline under the bedaquiline donation program needs to be reported to the NTP through aDSM mechanism. Data collection and reporting forms for the USAID Bedaquiline Donation Program is the same as for generic aDSM reporting. Practitioners involved in managing patients with bedaquiline need to follow the aDSM approach and report SAE to NTP, national medicines regulatory authority or the national pharmacovigilance centre in the country. Additional information in relation to the bedaquiline donation program can be accessed at the GDF website (http://www.stoptb.org/gdf/drugsupply/bedaquiline.asp). The use
of electronic databases is expected to hugely simplify the task to generate outputs and reports for different purposes from a consolidated source.

**Why do NTP and health care providers need to use the standard data dictionary if they are only going to analyse the data in the 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 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 drug-safety monitoring 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. You can also collaborate with international partners working in your country in the field of pharmacovigilance and introduction of new medicines (such as Challenge TB Project, SIAPS etc.)

**Is there software to analyse the questionnaire data?**

The USAID-funded SIAPS program provides a free web-based tool called PViMS for data collection, monitoring and analysis of adverse events as recommended for aDSM ([http://siapsprogram.org/tools-and-guidance/pvims/](http://siapsprogram.org/tools-and-guidance/pvims/)). PViMS tool is suitable for management and analysis of aDSM data in low and middle income countries. aDSM data collected from treatment sites can be analysed at the national level in collaboration with TB and drug safety monitoring authorities in-country to make quick evidence-based decisions to improve the safety of TB patients. Some national TB programmes are either expanding their existing electronic database for TB patients to accommodate the additional variables needed to collect data for aDSM; others are creating special databases solely for aDSM. When creating new systems it is important to ensure a good collaboration between the TB and drug-safety monitoring 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). Data from country-based information systems such as PViMS can be routed directly for integration in the global aDSM database.

**How do I create the drug safety profile?**

An outline of a drug safety profile is provided in Table 11.5 of Chapter 11 of the 2014 *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis*(11). 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. The elaboration and updating of drug safety profiles will be informed in part by evidence derived from the global aDSM database.
What are the indicators that NTP and health care providers need to report to WHO for patients on aDSM?

Five basic indicators are proposed (Table 2) and they are explained further in the 2014 Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis (11) (see in particular Table 11.5 in Chapter 11). For a number of them stratifications are recommended, such as by organ class or by seriousness. Out of the five indicators, the first and the third are considered essential to have in aDSM. As for all other aspects of aDSM, the indicators are primarily intended to help programmes assess the safety of the new medication and not solely as outputs to report to WHO.

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<tr>
<th>Indicator</th>
<th>Calculation</th>
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<tr>
<td>Target RR-/MDR-TB patients included in aDSM</td>
<td>Numerator: Number of TB cases started on target treatment included in aDSM during the period of assessment. Denominator: Number of TB cases started on target treatment during the period of assessment and who were eligible for aDSM.</td>
</tr>
<tr>
<td>Time to stopping target medicine</td>
<td>The difference in days between the date of start of treatment with a target medicine and the date of the stopping the target medicine. The calculation is done for each member of the cohort.</td>
</tr>
<tr>
<td>MDR/RR-TB patients included in aDSM with any serious adverse event</td>
<td>Numerator: Number of TB cases included in aDSM during the period of assessment with one or more serious adverse events. Denominator: Number of TB cases included in aDSM 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 aDSM. Denominator: Number of TB cases included in aDSM 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>
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Further reading


