Concept note

Global individual patient data platform for drug-resistant tuberculosis treatment (DR-TB-IPD)

Introduction

When compared with aggregated data, individual patient data (IPD) allows a more refined testing of hypotheses on the determinants of an outcome, with the potential for better adjustment for co-variates. This is exemplified by updates to the WHO treatment policy for drug-resistant tuberculosis (DR-TB) which has benefited from data from observational studies run in diverse settings worldwide, including data from national TB programmes, as well as data from randomised controlled trials. In fact, since 2010, meta-analyses based on progressively updated IPDs for both shorter and longer MDR-TB regimens and isoniazid-resistant TB treatment have informed successive WHO Guideline Development Groups when making recommendations on treatment regimen composition, duration and monitoring (1),(2),(3). In addition, this process has stimulated interest in the further exploration of IPD beyond the original scope of the guidelines, as well as the data analytical methods themselves (e.g. (4),(5)).

Early work to collect and analyse IPD for DR-TB treatment has been carried out by McGill University Health Centre (MUHC) in Canada working mostly to inform WHO or CDC/ERS/IDSA/ATS guidelines updates. Ahead of each guideline update, MUHC has undertaken a conventional systematic review of the literature and subsequently invited researchers to share data which was combined into the IPD. In 2018, the invitation was extended by WHO to contributions from published or unpublished studies via an open call in an effort to benefit from a more recent experience in the use of novel treatments in national TB programmes (6). Therefore, the IPD has been progressively updated over time, such that in 2020 it contains approximately 13,000 individual patient records, making it a substantial and informative dataset for policy making.

After each major update of the IPD, there have been several secondary uses of the data set, which have resulted in substantial new information and publications. In 2018, a committee to review and approve these secondary analyses was established. This committee was comprised of 6 representatives of *Data Owners*' group and a *Data Curator*[1]. This committee then reviewed a number of proposals and approved 6 projects for secondary analyses - most of which have been completed. However, a major problem of the IPD was that under the terms of the original data sharing agreements, signed between MUHC and all *Data Owner*s, all uses of the data remained strictly under the 'supervision' of the *Data Curator*. This allowed others to perform analyses of the data, but only under supervision, meaning physically at MUHC. This restricted access to the data and made it cumbersome for others to use it. Another problem of the IPD arrangements was that the access to IPD for analyses for the purposes of the WHO guidelines development and update, which is a well-recognized global public health good, was also restricted by the same process that is more appropriate for the data sharing with other individual researchers. With a gradual shift of WHO issuing public calls and data contribution from country programmes, a better and more transparent arrangements, data sharing and access regulations were needed.

[1] Norbert Ndjeka, JJ Yim, Peter Cegielski, Francis Varaine, Carole Mitnick, GB Migliori, and Dick Menzies representing McGill, Data Curator.

Definitions

DR-TB-IPD: Global individual patient data platform for drug-resistant tuberculosis treatment.

Data Curator: Entity in charge of maintenance, curation and hosting of the DR-TB-IPD.

Data Owner: an entity (country, institution or organisation) that submits Data into the DR-TB-IPD.

Data: All anonymized (i.e stripped of any personal identifiers) individual patient data (IPD) submitted or to be submitted to the DR-TB-IPD, from observational studies of patients with:

- multidrug resistant TB (MDR-TB), rifampicin-resistant TB (RR-TB), including more advanced forms of drug-resistance, such as extensively drug resistant TB (XDR-TB) and pre-XDR-TB;
- isoniazid-resistant TB (Hr-TB); and
- information on patients with any other form or pattern of drug resistance of interest.

Oversight Committee: coordinates the access to the DR-TB-IPD and is comprised of members from among *Data Owner*s, *Data Curator* and Global TB Programme of WHO.

Global individual patient data platform for drug-resistant tuberculosis treatment (DR-TB-IPD)

The DR-TB-IPD is a shared platform and collaborative initiative to generate reliable evidence on the drug-resistant TB treatment to inform future tuberculosis treatment guidelines. It is supported by the WHO Global TB Programme (GTB) and maintained by the selected *Data Curator*.

The purpose of the DR-TB-IPD is to facilitate pooling of individual patient data issued from researchers, local or national databases in the context of DR-TB treatment and facilitate policy update, development and public health research.

The access to the DR-TB-IPD for analyses not related to the WHO guidelines development is coordinated by an *Oversight Committee* comprising members from among *Data Owner*s, *Data Curator* and GTB. Countries, surveillance projects and researchers are regularly invited to contribute data.

Objectives of the *DR-TB-IPD*

General objective:

To establish a shared resource of up-to-date, well-maintained and accurate IPD from observational and intervention studies and/or programmatic data from countries on treatment of drug-resistant TB (DR-TB) that will facilitate high quality conduct of, and training in, research in treatment of DR-TB and contribute to the development of the new treatment recommendations.

Specific objectives:

- To assemble high quality, anonymized individual level data on patients with DR-TB, that will allow detailed analyses of correlates of treatment outcomes.
- To enable access to the DR-TB-IPD for review and systematic analyses for the purpose of WHO guidelines development—a global public health good.

- To enable access to the DR-TB-IPD for review and systematic analyses to external researchers for not-for-profit/non-commercial purposes.
- To support training in analysis, including advanced meta-analytic techniques, of large-scale datasets for trainees from low- and middle-income countries, who are employed by national programs, non-government organizations, or academia in those countries.

Scope of analytic work:

1. Treatment correlates of outcomes of all forms of DR-TB treatment. For example, the association of individual drugs such as bedaquiline or delamanid, or the number of effective drugs or the duration of treatment with treatment success.
2. Adjunctive treatment measures and their association with treatment outcomes. For example, use of directly observed treatment, or surgery.
3. Drug resistance patterns as correlates of treatment outcomes as clinical validation of drug-susceptibility testing.
4. The association between patient and disease characteristics with treatment outcomes, such as AFB smear, cavitation on chest x-ray, HIV co-infection, previous treatment and drug resistance pattern.
5. Analysis for other purposes not specified above when WHO and the collaborators deem to be relevant and within the spirit of the IPD.

Principles of the *DR-TB-IPD*

1. The data are anonymized, and no identification of the individual patient's identity can be made at any time. This includes ensuring that, in the analysis, particularly of small groups, individual identities cannot be inferred from presentation of the results. The institutions/groups contributing data will be apparent in the data set to anyone performing analysis, and the identity of institutions/groups may be revealed in descriptive analyses. However, analytic results such as correlates of treatment outcomes, nor specific treatment outcomes (e.g. failure/relapse/death) will not be reported at the level of countries, institutions or groups contributing data.
2. The data contributed continues to be owned by the individual, group, country or institution that has contributed the data. This also means the data can be withdrawn from the DR-TB-IPD at any time.
3. The data are to be shared for use, under certain conditions and after approval by an *Oversight Committee*. This means that, after a process of review and approval, the data can be accessed for analysis by contributing members of the DR-TB-IPD as well as other not-for-profit organizations, institutions or National TB programs.
4. For the specific purpose of WHO guidelines development—a global public health good—data sharing will not require review by the *Oversight Committee* or individual *Data Owner*s. It should be clear that the statistical analysis plans, including specific questions or objectives are determined by the Guidelines Development Groups (GDG) convened by WHO.
5. Access to the data for all other uses, and for any analyses that will lead to eventual publication (other than publication of WHO guidelines) will be regulated by an *Oversight Committee*

comprised of four representatives of *Data Owner*s, the *Data Curator* and WHO. The representatives of the *Data Owner*s will be elected by all *Data Owner*s (one vote per group/organization contributing data). Individuals, groups, or organizations who wish to analyze the data shall submit a brief application (maximum 2 pages) to the *Oversight Committee*. If granted access they shall abide by strict rules governing the use of the data (see below for details).

6. The data shall not be used for profit, nor sold to any third party. If the data are provided to an individual, group or institution, they cannot in turn provide the data to any other individual, group or institution.
7. Data will be accurate and of the highest possible quality. The individual, group, or institution contributing data remains responsible for the accuracy of the data submitted. The *Data Curator* will take all measures to ensure that the quality is improved through coherency checks and other quality assurance measures in place to safeguard the wholesomeness of the data.
8. Queries about the data will be sent to the *Data Curator*, who may choose to refer the questions to the original *Data Owner*s. There will not be any direct queries between data analysts and *Data Owners.* This will ensure that any additions or corrections to the data are well documented, and that the DR-TB data base is as accurate and up-to-date as possible, and that at any time, there is only one 'correct' version of the data-base.
9. The bioethics review board that oversees the institution that is serving as the *Data Curator* will also review the uses of data.
10. Data will be kept in a secure environment so that it cannot be accessed except through the *Data Curator*, who will release the data to users after approval by the *Oversight Committee* through a secure means without necessitating that the requestor of the data travels to the physical location where the *Data Curator* is based. Details about this and about destruction of data after use will be provided separately.

Procedures for contributing data to the *DR-TB-IPD*.

1. **Data contribution.** Country program, academic institution or individual with data interested in contributing to the DR-TB-IPD can contact WHO, or the *Data Curator*, or any member of the DR-TB-IPD OC. There will be a preliminary discussion with *Data Owner* regarding the type and number of patients, type of DR-TB, information available and treatment outcomes.
2. **Data Sharing Agreement (DSA).** If the data appears eligible for inclusion in the DR-TB-IPD, a data sharing agreement will be executed between the *Data Owner* (individual or institution) and the *Data Curator*.
3. **Data transfer.** The *Data Curator* will send to the *Data Owner* detailed instructions, including standardized database template and data dictionary regarding how to format the data so they can most easily merge with the existing DR-TB-IPD.[2] If the *Data Owner* does not have sufficient technical capacity to format the data to the common standard, then the *Data Curator* may undertake formatting - in specific instances and based on mutual agreement and when relevant resources are available. The data will be sent by secure file transfer. When received

[2] For a description see: Campbell JR, Falzon D, Mirzayev F, Jaramillo E, Migliori GB, Mitnick CD, et al. Improving Quality of Patient Data for Treatment of Multidrug- or Rifampin-Resistant Tuberculosis. Emerg Infect Dis. 2020;26(3). Available from: http://wwwnc.cdc.gov/eid/article/26/3/19-0997_article.htm

by the *Data Curator* it will be checked for completeness and also variable names and definitions.

4. **Data merge**. When data is merged into the DR-IPD, an update will be posted that reflects the date the data were added, the number of individual patient records, type of DR-TB, and the WHO region of origin of the *Data Owner*(s).
5. **Data source attribution**. Once the data are available, and used, then acknowledgement of the data sources must be made in all public presentations or publications.

Oversight of use of the data of the *DR-TB-IPD*

1. The DR-TB-IPD will have oversight by an *Oversight Committee* of 6 members. Four of the committee members will be representatives of the *Data Owner*s, elected by the contributors by a majority vote. Effort will be made to ensure there is approximately equal representation of low- and middle-income and high-income countries, as well as national programs/public health and academia among committee members. These members of the committee can be self-nominated and will be elected by a majority vote from all *Data Owner*s (1 vote per individual/institution that contributed the data) for 5 years.
2. This *Oversight Committee* will also include a representative from the WHO Global TB Programme (voting), plus a non-voting representative of the *Data Curator*. This last member, the *Data Curator*, will advise on feasibility and data completeness and quality issues related to the statistical analysis plan (SAP).
3. Any individual or group who wishes to analyze the DR-TB-IPD must submit a summary SAP to the *Oversight Committee*. This plan would outline the objectives, research questions, key variables, analytic methods, anticipated methodologic issues, and how they will be addressed, analytic methods, and a dissemination plan. However, it should be brief, and entail no more than two pages. The *Data Curator*s may offer support to groups developing their SAP - to strengthen the application.
4. The SAP will be reviewed by the *Oversight Committee* that will approve, request revisions, or reject. Rejection can be because the proposal is viewed to be not scientifically sound, or not feasible with the available data. A written response to each request must be made, within 30 days. Detailed reasons for rejection (if applicable) will be provided in that response. Suggestions for improvement may also be made if the request is approved, but these are not obligatory. Requestors can revise and re-submit.
5. The committee shall seek to achieve consensus on every decision. If consensus cannot be reached, then it will be by simple majority. The *Data Curator* representative will not vote.
6. Those who are eligible to access and analyze the data include:
    - All those that have contributed data to the DR-TB-IPD, including past contributors
    - Other academics, NGOs, national TB programmes or national agencies
    - International agencies.
7. Not eligible: individuals from for-profit companies (e.g. pharmaceutical companies).

Maintenance of the DR-TB-IPD

Since IPD inception, the *Data Curator* was the McGill TB Centre, of the McGill University Health Centre (MUHC). Each subsequent *Data Curator* will be selected by WHO for a period of 5 years. The

requirements to continue to host, maintain, accrue new records, and curate the DR-TB-IPD to the high standards of quality and comprehensiveness will be defined in a budgeted 5-year plan by the *Data Curator*. This activity will be a key step to ensure the stability of the database given that it is increasingly recognised as a key resource for evidence-based guidance in DR-TB treatment. Both *Data Curator* and the WHO Global TB Programme will be expected to contribute to this resource and will seek funding from external agencies for its continued support.

References

1. Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 Update. (WHO/HTM/TB/2011.6) [Internet]. Geneva, World Health Organization. 2011. Available from: http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf
2. WHO treatment guidelines for drug-resistant tuberculosis, 2016 update (WHO/HTM/TB/2016.4) [Internet]. Geneva, World Health Organization. 2016. Available from: http://apps.who.int/iris/bitstream/10665/250125/1/9789241549639-eng.pdf
3. WHO consolidated guidelines on drug-resistant tuberculosis treatment (WHO/CDS/TB/2019.7) [Internet]. Geneva, World Health Organization. 2019. Available from: https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf
4. Fox GJ, Benedetti A, Mitnick CD, Pai M, Menzies D, The Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB. Propensity Score-Based Approaches to Confounding by Indication in Individual Patient Data Meta-Analysis: Non-Standardized Treatment for Multidrug Resistant Tuberculosis. Brock GN, editor. PLOS ONE. 2016 Mar 29;11(3):e0151724.
5. Walker IF, Shi O, Hicks JP, Elsey H, Wei X, Menzies D, et al. Analysis of loss to follow-up in 4099 multidrug-resistant pulmonary tuberculosis patients. Eur Respir J. 2019 Jul;54(1).
6. WHO | Public call for individual patient data on treatment of rifampicin and multidrug-resistant (MDR/RR-TB) tuberculosis [Internet]. WHO. [cited 2018 Feb 27]. Available from: http://www.who.int/tb/features_archive/public_call_treatment_RR_MDR_TB/en/

Annex. Key principles of the Data Sharing Agreement

- The data are to be shared for use, under certain conditions and after approval by an Oversight Committee. This means that, after a process of review and approval, the data can be accessed for analysis by contributing members of the DR-TB-IPD as well as other not-for-profit organizations, institutions or National TB programs.
- For the specific purpose of WHO guidelines development—a global public health good—data sharing will not require review by the Oversight Committee or individual Data Owners.
- Access to the data for all other uses, and for any analyses that will lead to eventual publication (other than publication of WHO guidelines) will be regulated by an Oversight Committee comprised of four representatives of Data Owners, the data curator and WHO. The representatives of the Data Owners will be elected by all data Owners (one vote per group/organization contributing data). Individuals, groups, or organizations who wish to analyse the data shall submit a brief application (maximum 2 pages) to Oversight Committee. If granted access they shall abide by strict rules governing the use of the data.