Title
Clinical standards for the assessment, management and rehabilitation of post-TB lung disease

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Clinical standards for the assessment, management and rehabilitation of post-TB lung disease

SUMMARY

BACKGROUND: Increasing evidence suggests that post-TB lung disease (PTLD) causes significant morbidity and mortality. The aim of these clinical standards is to provide guidance on the assessment and management of PTLD and the implementation of pulmonary rehabilitation (PR).

METHODS: A panel of global experts in the field of TB care and PR was identified; 62 participated in a Delphi process. A 5-point Likert scale was used to score the initial ideas for standards and after several rounds of revision the document was approved (with 100% agreement).

RESULTS: Five clinical standards were defined: Standard 1, to assess patients at the end of TB treatment for PTLD (with adaptation for children and specific settings/situations); Standard 2, to identify patients with PTLD for PR; Standard 3, tailoring the PR programme to patient needs and the local setting; Standard 4, to evaluate the effectiveness of PR; and Standard 5, to conduct education and counselling. Standard 6 addresses public health aspects of PTLD and outcomes due to PR.

CONCLUSION: This is the first consensus-based set of Clinical Standards for PTLD. Our aim is to improve patient care and quality of life by guiding clinicians, programme managers and public health officers in planning and implementing adequate measures to assess and manage PTLD.

KEY WORDS: tuberculosis; post-TB lung disease; sequelae; pulmonary rehabilitation; clinical standards

Historically, national TB programmes (NTPs) have emphasised the need to ensure rapid diagnosis and effective treatment of individuals with infectious TB to reduce transmission and the epidemiological trend of the disease.[1,2] Over the past 20 years, the number of individuals successfully treated for TB has increased substantially, with an estimated 155 million TB survivors alive in 2020.[3,4] However, a substantial proportion of people considered cured (or with TB treatment completed) report residual cough, weakness, dyspnoea, difficulties in climbing stairs or managing every-day or work activities, which affect their quality of life (QoL) and increase the risk of death.[5–10] These long-term sequelae from TB treatment are identified using a series of tests, including chest imaging (e.g., fibrosis, cavities, pleural thickening, bronchiectasis, pulmonary hypertension, secondary bacterial and fungal infections); pulmonary function testing (PFT), including spirometry, plethysmography and diffusing capacity of the lungs for carbon monoxide (DLCO) to detect obstructive, restrictive and mixed patterns; and cardiopulmonary exercise testing (CPET) to assess the integrative responses of the cardiovascular, respiratory and musculoskeletal systems to incremental exercise in patients with PTLD.[11–20]

Delayed diagnosis and inappropriate regimens used during treatment may play a role in the development of PTLD.[21,22] Also, former TB patients experience increased non-pulmonary morbidity and mortality, particularly cardiovascular diseases, despite successful completion of treatment.[23,24] The aetiology of these illnesses is uncertain, but they may in part reflect the systemic effects of sustained lung inflammation and enzymatic degradation, which persist after TB cure.[25,26] Moreover, individuals who previously completed TB treatment continue to be at high risk of developing TB again due to either endogenous reactivation or exogenous reinfection.[27,28] Distinguishing between recurrent TB vs. post-TB sequelae can be particularly challenging.[29–31]

For this document, we adopted the definition of PTLD developed at the First International Symposium on Post-TB disease: "Evidence of chronic respiratory abnormality, with or without symptoms attributable at least in part to previous (pulmonary) tuberculosis".[32] In recent years, PTLD has attracted increasing interest from the research and medical community. Several studies indicate that up to 50% of TB patients report health problems consistent with PTLD after completion of treatment.[11–13,33–38] PTLD is likely to cause a considerable burden of disease globally, suggesting opportunities for prevention and management. Recent modelling indicates that 138–171 million TB survivors were alive in 2020, of whom nearly one fifth were treated in the past 5 years.[4] PTLD was estimated to account for approximately half of lifetime disability-adjusted life-years (DALYs) caused by incident TB.[38–40]

In preparing this document, our aim was to define clinical standards for PTLD, focusing primarily on pulmonary disease. Standards are different from guidelines, which are based on 'Grading of Recommendations, Assessment, Development, and Evalua-

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tion' (GRADE) and 'Patient, Intervention, Comparison, Outcome (PICO) questions. Standards prescribe a widely accepted level of diagnosis and care, for all healthcare providers and clinicians, both public and private, to achieve optimal standards in managing patients who have, or who are presumed to suffer from, a given disease.[41,42] The IJTLD Clinical Standards do not compete with existing WHO or other guidelines, but rather complement and integrate their recommendations to provide a specific clinical focus. The standards are universal principles and might need to be adapted for specific settings and situations for future programmatic implementation due to legal, organisational or economic reasons.

Because specific evidence on PTLD is limited in some technical areas, the available evidence on other lung diseases was used (e.g., for chronic obstructive pulmonary disease [COPD]), although such studies exclude patients with TB. Also, research into paediatric care is currently limited, but recommendations were added where appropriate. The clinical standards will be updated to capture new evidence as it accumulates over time. Finally, although these standards pertain to evaluations and interventions after a patient has completed TB treatment, a small but growing body of research indicates that patients at risk for PTLD can be identified using chest radiography (CXR) at the time of TB diagnosis.[43] The use of adjunctive therapies during TB treatment may therefore help to avert PTLD or reduce its impact.[44,45] Physicians are urged to consider such at-risk patients for enrolment in clinical trials to expand our understanding of this area.

AIM OF THE CLINICAL STANDARDS

This consensus-based document aims to describe the following activities:

1) Assessing patients at the end of TB treatment for sequelae and PTLD (Standard 1). A universal standard was defined, with special considerations for children and possible adaptation in different settings and situations (for organisational, legal or economic reasons).
2) Identifying patients with PTLD for pulmonary rehabilitation (PR) (Standard 2).
3) Adapting the PR programme for specific patient needs and different settings (Standard 3).
4) Evaluating the effectiveness of PR and follow-up (Standard 4).
5) Education and counselling for a patient (Standard 5) to help manage their condition.
6) A public health standard highlighting the need to record changes in patient outcome resulting from PR (Standard 6).
7) Priorities for future research into PTLD.

METHODS

A panel of 67 global experts was identified to represent the main scientific societies, associations and groups active in the field of TB and PR, including TB clinicians ($n = 34$), TB public health ($n = 18$), TB paediatricians ($n = 3$), PR experts ($n = 6$), PFT/lung diseases experts ($n = 3$), methodologists ($n = 2$) and psychologist ($n = 1$). Out of the 67 experts invited, 3 declined and 2 did not respond. The 62 respondents were asked to comment via a Delphi process on an initial draft including seven standards (Standards 1–6 being clinical and Standard 7 on public health) developed by a core coordination team (with 17 members). A 5-point Likert scale was used (5: high agreement; 1: low agreement). Sixty experts submitted a valid Delphi questionnaire (two did not answer). At the first Delphi round, agreement was high, with a median value of 5 for Standards 1–6, and 4 for Standard 7. Based on substantial agreement on the seven Standards and the document outline, a draft document was jointly developed by the expert panel. This underwent seven rounds of revision and the final form was approved by consensus (100% agreement), with a reduction in the number of standards to 6 in total (5 clinical and 1 on public health).

STANDARD 1

Every patient completing TB treatment should be clinically evaluated for PTLD. The assessment should be conducted as soon as possible at the end of treatment and organised by the TB programme. In special settings and situations, post-TB treatment evaluation can be simplified and/or modified to include a set of basic examinations with the aim to identify patients with sequelae at risk of deterioration (or even death) and those likely to benefit from PR. The following set of basic examinations is considered essential upon clinical suspicion of either the presence of, or risk factors for, PTLD: clinical examination/history, CXR, PFT, six-minute walking test (6MWT), complemented by symptom score and QoL questionnaire evaluation. Other examinations are considered conditional.

The complete list of examinations to assess the presence of post-TB treatment sequelae and the indications for PR (see Standards 2–3 for details) are summarised in Table 1. Completion of treatment affords the opportunity to (safely) evaluate the patient's microbiological and radiological status, and the relationship with baseline assessments. Although the focus of this document is on PTLD, it is important to note that bacteriological results (sputum smear microscopy and culture) are important at diagnosis, during follow-up and at the end of treatment to determine the TB treatment outcome

Table 1 Standard 1: Recommended examinations to be conducted at the end of treatment and in special settings and situations because of legal, organisational or economic reasons

	Essential and conditional examinations/investigations	Adaption for special settings and situations
Clinical assessment	• Clinical history, symptom assessment and clinical examination	• Clinical history, symptom assessment and clinical examination
Imaging	• Chest radiography (digital) • Computed tomography	• Chest radiography
Functional evaluation	• Spirometry, including pre- and post-bronchodilator test • Plethysmography • Diffusion capacity assessment (DLCO, KCO) • Tidal breathing techniques (oscillometry/MBW) • Arterial blood gas analysis, and pulse oximetry (SpO_2) • 6MWT • CPET	• Spirometry • SpO_2 • 6MWT
Subjective evaluation	• QoL questionnaire • Frequent symptoms score	• QoL questionnaire • Frequent symptoms score

DLCO = diffusing capacity of the lungs for carbon monoxide; KCO = carbon monoxide transfer coefficient; MBW = multiple breath washout; SpO_2 = peripheral capillary oxygen saturation; 6MWT = six-minute walking test; CPET = cardiopulmonary exercise testing; QoL = quality of life.

(cured or treatment completed, see also Standard 6).[46] CXR is also important. Computed tomography (CT) scan, which is not always available, allows a more thorough evaluation of the lung parenchyma that is often not visible (or fully appreciated) on CXR. For example, it may offer higher sensitivity to detect bronchiectasis, cavities or pulmonary nodules as a basis to improve current and future clinical management (sputum expectoration, risk of recurrent infection, risk of chronic fungal infection and risk of TB relapse). Pulmonary nodules may be a consequence of TB but can also represent other infections or cancer.[47] The advantages of a CT scan must be weighed against the harms of radiation exposure. Use of CT scans should therefore be reserved for instances when differential diagnostic imaging beyond CXR is highly desirable to inform clinical decision making. In patients with cavitary TB, who develop progressive respiratory symptoms after treatment completion, additional testing may be warranted to evaluate for TB relapse, chronic infections (aspergilloma, non-tuberculous mycobacteria [NTM] infections, bronchiectasis) and other lung disease (e.g., cancer). Further investigations may include chest CT, culture of sputum or fluid collected by bronchoalveolar lavage (e.g., for *M. tuberculosis,* Aspergillus and other respiratory pathogens) and Aspergillus serology.[48] In settings with sufficient resources, additional assessments would add important clinical and functional information to PTLD management, particularly as it relates to lung health (for details on rehabilitation, see Standards 3–4) and mortality risk.

A focused respiratory history needs to be recorded including vaccination history (e.g., COVID-19, influenza, pneumococcal vaccines), risk factors (e.g., previous incarceration) and co-morbidities (e.g., HIV co-infection and diabetes, among others) as well as exposure to health hazards (such as cigarette smoking, silica and biomass fuel). Known respiratory co-morbidities and related previous treatments for any lung condition also need to be recorded, as these are likely to be relevant for the management of PTLD. Examples include asthma, bronchiectasis, pulmonary fibrosis and COPD as well as a history of pulmonary TB (PTB) and/or frequent lower respiratory tract infections in childhood.

A clinical examination at the end of TB treatment, when performed thoroughly, helps guide appropriate further investigations. Recordings for weight, height and vital signs (temperature, respiratory and heart rates, blood pressure and oxygen saturations) is considered essential. The presence of low arterial oxygen saturations (<94%, ideally complemented by arterial blood gases analysis, if feasible), changes in body mass index (BMI) and its trend over time, digital clubbing, coarse crackles, raised jugular-venous pressure or peripheral oedema may suggest pathology other than TB or concurrent pathologies. A subsequent nutritional assessment includes, among others,[49] simple investigations (e.g., urine analysis and blood tests) to identify treatable conditions that commonly cause morbidity.[50] For example, anaemia caused by iron deficiency can be diagnosed by blood tests and is amenable to oral supplementation, and unexpected glycosuria could lead to a diagnosis of diabetes. Desirable blood tests include complete blood count with white cell differential, fasting blood glucose, electrolytes, urea, creatinine and liver function tests, including serum albumin. Unexplained or persistent biochemical abnormalities should be complemented by the appropriate investigation (or referral) to diagnose and treat the underlying condition. Comorbid medical conditions associated with TB that are known to increase mortality, particularly if untreated, should be noted. These include but are not limited to HIV, diabetes mellitus, chronic kidney diseases, chronic liver diseases (including chronic hepatitis B and C), anaemia and iron deficiency.[11,32,50] Recently, the importance of COVID-19 has also been highlighted, and opportunities

exist to combine efforts supporting rehabilitation approaches for patients with both TB and COVID-19 related sequelae.[51–54]

Given the high rates of PTB and the body of evidence linking TB with chronic respiratory diseases (CRDs), PFT should be routinely performed on completion of TB treatment in all settings where it is available and compared with previous PFT results. For example, pre- and post-bronchodilator spirometry performed according to the European Respiratory Society (ERS)/American Thoracic Society (ATS) standards,[55] with appropriate equipment provides essential information on lung function and is the diagnostic test of choice for CRDs. When feasible and available, spirometry can be complemented by plethysmography (to assess total lung capacity and resistance), DLCO or carbon monoxide transfer coefficient (KCO) to assess ventilatory inhomogeneity for comprehensive assessment of lung function.[11,32]

The six-minute walking test (6MWT), performed according to international guidelines, is a simple tool largely used to evaluate functional exercise capacity, assess prognosis and evaluate treatment response in CRDs.[56] The 6MWT is generally considered reliable for chronic respiratory diseases and requires limited resources.[11,32] Furthermore, the 6MWT is useful for the evaluation of exercise-induced desaturation as assessed using pulse oximetry (SpO2), although the reference values to be used may be an issue. Clinical examination might justify the need for additional investigations in specific patients, for example, echocardiography to evaluate pulmonary hypertension and secondary right heart failure, or evidence of lesions that put patients at risk of spontaneous pneumothorax (or history of previous pneumothorax) or of possible broncho-pleural fistula. Similarly, some patients may benefit from assessment of cardiovascular risks, including determination of blood lipids, C-reactive protein and N terminal pro brain natriuretic peptide (Nt-proBNP).

The persistence of symptoms such as breathlessness or cough are associated with disease progression, contributing to a decline in physical function and health-related QoL. Therefore, the evaluation should include the subjective perception of symptoms and the corresponding impact on daily life. There are numerous questionnaires validated for use in subjects with CRDs, although not PTLD specifically. It is recommended that questionnaires are administered by trained personnel, when needed, respecting their specific indications. The choice of the questionnaire or scales also depends on the time available and the education level of the patient.

Specific considerations for paediatric care

Despite increasing global awareness of PTLD, there is a lack of data for children. Numerous cohort studies have shown that there is an association between lung function in childhood and adulthood. PTB in childhood could therefore have long-lasting consequences on lung health later in life.[57,58] A better understanding of the impact of PTB on long-term respiratory morbidity in children is therefore urgently needed. End of TB treatment assessment should follow standards as proposed in adults, with some considerations specific to children. Just over half of children diagnosed with TB will have a clinical diagnosis ("unconfirmed TB cases") and no microbiological confirmation due to the often paucibacillary nature of paediatric TB.[59] This results in the majority of children having an outcome of "treatment completed" instead of "cured". Radiological imaging can be considered at the end of treatment for use as a comparative tool in case TB recurs. CT scans of the chest are usually not indicated due to challenges of investigation in children and radiation exposure, but can be considered in specific cases (substantial chronic symptoms and radiological abnormalities) to evaluate the extent of PTLD or exclude a different diagnosis.

Lung function should be considered in all children with severe TB lung involvement[60] over the age of 4–6 years, and include pre- and post-bronchodilation flow/volume curves. Tidal breathing techniques, including forced oscillometry and multiple breath washouts, can be considered in children younger than 4 years of age. Data on lung function impairment in children is currently lacking and is a priority for research.

Quality of life questionnaires such as EQ-5D-Y and Toddler and Infant (TANDI) can be used to assess health-related QoL in children – although these need local adaptation for the youngest children. Functional exercise capacity can be measured using the 6MWT in children from the age of 4 years. Reference ranges were established in a Caucasian population and might require adaptation in different settings.[61]

STANDARD 2

Evaluation for PR. Former TB patients with clinical and radiological signs and symptoms consistent with post-TB treatment sequelae, evidence of obstruction and/or restriction, desaturations and/or low oxygen levels, reduced exercise tolerance and related impairment in quality of life should be evaluated for PR.

PR is a core component in the management of CRDs and is described as an 'individually tailored and designed, multidisciplinary programme of care' for patients with chronic respiratory impairment.[62] There is strong evidence that PR improves health status, exercise capacity, fatigue, and social functioning, and is recommended in international guidelines.[63,64] There is currently a lack of data in children, but tools used in children with other chronic respiratory illnesses can also be used in paediatric PTLD. Growing evidence indicates that PTB causes

Table 2 Standard 2: Indications for pulmonary rehabilitation[69–84]

Indications	Essential and conditional examinations/investigations	Adaption to special settings and situations
Pulmonary rehabilitation should be evaluated in all cases of TB cured (smear- or culture-negative in the last month) and TB treatment completed with:		
Impaired exercise capacity[32,56,69,70]	• Cardiopulmonary exercise test and/or • Six-minute walking test and/or • Five repetition sit to stand test and/or • Maximal voluntary contraction	• Six-minute walking test and/or • Five repetition sit to stand test
Reported respiratory symptoms (dyspnoea, cough, sputum, wheeze, chest pain, fatigue)[71–74]	• Modified Medical Research Council • Modified Borg Scale • Visual Analogue Scale	• Modified Medical Research Council • Modified Borg Scale • Visual Analogue Scale
Presence of comorbid conditions, including chronic obstructive pulmonary disease, asthma, bronchiectasis, pulmonary fibrosis, pulmonary hypertension, and/or need for surgery[12,13,75]	• Clinical history • Diagnostic test or examinations	• Clinical history • Diagnostic test or examinations
At least 1 hospitalisation or 2 exacerbations in the last 12 months[11,32,76,77]	• Clinical history	• Clinical history
Impaired pulmonary function showing airflow obstruction or restriction or mixed abnormalities and bronchodilator response and/or impaired diffusing capacity for carbon monoxide[78]	• Spirometry with plethysmography, if available • Diffusing capacity for carbon monoxide	• Spirometry
Abnormal blood gas PaO_2 <80 mmHg/10.6 kPa and/or $PaCO_2$ >45 mmHg/6.0 kPa and/or nocturnal and exercise-induced desaturation[79]	• Blood gas analysis and/or • Pulse oximetry	• Pulse oximetry
Ineffective cough and/or difficult to clear bronchial secretions[80,81]	• Clinical examination and/or • Lung function tests (reduction of vital capacity <1.5 L and/or reduction of peak cough flow <160–200 L/min and/or reduction of maximal inspiratory pressure and/or reduction of maximal expiratory pressure)	• Clinical examination
Impaired quality of life[82–84]	• TB-specific questionnaire: EUROHIS-QOL 8 ≤16 • Disease specific questionnaire: SGRQ >25 • Generic questionnaire WHOQOL-BREF <60 (subjects aged ≥60)	• TB-specific questionnaire: EUROHIS-QOL 8 ≤16 • Disease-specific questionnaire: SGRQ >25 • Generic questionnaire WHOQOL-BREF <60 (subjects aged ≥60 years)

EUROHIS-QOL = European Health Interview Survey-Quality of Life; SGRQ = St George's Respiratory Questionnaire; WHOQOL-BREF = abbreviated World Health Organization Quality of Life.

CRD in a proportion of patients with lung damage at different levels: in the bronchial airways (e.g., non-reversible airflow obstruction, bronchiectasis, trachea-bronchial stenosis) and in the lung parenchyma (cavities, fibrosis, restrictive lung disease); it can also cause mixed patterns.[11,65–67]

The severity of pulmonary sequelae is usually related to a delay in diagnosis or treatment and/or inadequate/inappropriate treatment, leading to extensive lung damage and longer treatment duration, likely to be more evident in patients with multidrug-resistant or extensively drug-resistant TB or TB relapse/recurrence.[11,12] Although adequate clinical and radiological evaluation of patients at the beginning of anti-TB treatment and during treatment monitoring can identify initial sequelae, the end of treatment provides an opportunity to adequately study the patient without risk of infection for family members, health staff or other contacts.[7,63,68] A careful patient assessment at the end of TB treatment (patient cured or with treatment completed) is needed to evaluate if there are indications for PTLD and therefore if such patients would potentially benefit from PR. After excluding cardiovascular risks, PR is an appropriate measure for patients with persistent symptoms (dyspnoea, chest pain, cough, muscular fatigue), or reduced exercise tolerance, a restriction in activities because of their disease, exercise-induced oxygen desaturation, or impaired health status.

A comprehensive assessment should be performed in order to detect and quantify the possible impairment due to PTLD (see Standard 1).[11,12,32] The assessment (see Table 2[69–84]) should focus on TB sequelae and their functional impact, as well as on pulmonary interventions needed (e.g., long-term oxygen therapy, ventilation) and include radiological aspects, spirometry findings and bronchodilator response, assessment of lung volumes, DLCO, arterial blood gases, nocturnal and exercise-induced desaturations, 6MWT and QoL. PR (specifically covered in Standards 3–4) is a comprehensive package of interventions, which can include exercise, education, nutrition, self-management activities and psychosocial support.[85]

STANDARD 3

The PR programme should be organised according to feasibility, effectiveness and cost-effectiveness criteria, based on the local organisation of health services and tailored to the individual patient's needs.

Most of what is known about PR is derived from CRDs, where it has been shown to be relatively more cost-effective than pharmacotherapy.[86] Obviously, there are differences between these conditions and PTLD, and important evidence gaps are highlighted in this document. To qualify as PR, programmes must include, at the very least, comprehensive baseline and post-PR outcome measurements, a structured and supervised exercise training programme, an education/behavioural programme intended to foster long-term health-enhancing behaviour, and provision of recommendations for home-based exercise and self or supervised physical activity programmes.[87]

Evidence on specific PR programmes tailored to PTLD patients exists in settings with adequate resources, logistics, and expert healthcare providers – and these were generally effective.[88–91] At the same time, simplified programmes with no need for major capital outlay and equipment were successfully adapted and applied to specific circumstances without hampering the activities of the NTP.[92,93] The possibility of modulating PR programmes by adapting them to the context and resources available (to prevent unmanageable workload), makes PR potentially accessible to individuals (including children and adolescents) in different settings.[12,92,94–99] The core components of a PR programme are summarised in Table 3.[100–109]

STANDARD 4

Evaluating the effectiveness of PR for former TB patients. The standard includes a short description on how to evaluate the effectiveness of PR by comparing the core variables before and after rehabilitation. The standard also suggests how to organise follow-up for the patient.

As discussed in Standard 1 and 2, on completion of TB treatment and before starting a PR programme tailored to a patient's needs, a comprehensive assessment is necessary. The easiest way to evaluate the effectiveness of PR is to assess the core variables 'at the end' vs. 'at the beginning' of the programme,[88–90,92] as summarised in Table 4. As a minimum, the patient's functional exercise capacity, dyspnoea and health status should be assessed.[11,12,32]

Recently, a list of health outcomes including social, economic and psychological impact has been recommended as a core component of the evaluation.[11,32] The measure of exercise capacity most frequently used is the 6MWT.[88–90,95] However, the cardiopulmonary exercise test or the incremental shuttle walk test and the 5 repetition sit to stand test are also applied.[70,92] PR in PTLD patients has been shown to significantly improve the distance covered during the 6MWT (by approximately 35–45 m), an improvement similar to that recorded in subjects with COPD.[110] QoL was evaluated by questionnaires, all different from each other, and no study used disease-specific questionnaires. However, the results seem to confirm significant improvement when QoL was evaluated using the St George's Respiratory Questionnaire, Short Form Health Survey 36 and Clinical Chronic Obstructive Pulmonary Disease questionnaire.[111,112] Similarly, the symptom evaluation was conducted for dyspnoea, chest pain, haemoptysis and cough by using different scales.

No data are available on other strong outcomes such as mortality and morbidity. It is desirable to use validated and shared tools to consolidate knowledge on PR for PTLD.

Follow-up

Follow-up is desirable for patients undergoing PR to assess if any clinical problem has arisen, and to ensure that the benefits achieved after PR are maintained. The follow-up needs to be organised based on local feasibility and organisation of health services. Individuals who complete an episode of TB treatment, especially those with residual pulmonary sequelae (e.g., residual cavitation) and with other infections (e.g., aspergilloma and NTM) remain at elevated risk of TB.[29,30] Recurrent TB may be due to endogenous reactivation or exogenous reinfection[27,28] and is frequently observed, particularly in settings with a high incidence of TB.[113,114] Follow-up should therefore include appropriate measures to detect recurrent TB at an early stage and refer individuals with disease recurrence for prompt treatment. Recurrent TB can be identified based on clinical or radiographic findings, in addition to microbiological evidence, after excluding other causes (NTM, fungal or other chronic bacterial infections).

If feasible, follow-up of patients with sequelae not requiring (or with contra-indications for) PR can also be considered. Table 5 includes a generic scheme for follow-up visits. Considering the risk of recurrence, infection control and prevention measures and re-assessment of the patient's potential contagiousness are recommended during all steps of the process.

STANDARD 5

Each patient completing PR should undergo counselling/health education, including a follow-up plan to maintain/improve the results achieved, organised according to feasibility and cost-effectiveness criteria, based on the local organisation of health services and tailored to the individual patient's needs.

Table 3 Standard 3: Summary of the core components of a rehabilitation programme[100–109]

		Methods	
Components	Indication	Interventions	Adaption to special setting and situations
Aerobic exercise: endurance training	Impaired exercise capacity, limited by dyspnoea and or other respiratory symptoms Restriction in daily life activities.[11,32]	• Treadmill and/or cycle-ergometer • 30 min 2–5 times/week for 4–8 weeks • Intensity set according to maximal oxygen consumption or the equation of Luxton or 80% of heart rate max adjusted on dyspnoea • In or out-patients or tele-monitoring • Suggest maintenance programme	• Free walking • 30 min 2–5 times/week for 4–8 weeks • Intensity set according to perceived dyspnoea • Outpatients or home setting • Suggest maintenance programme
Strength training: upper and lower extremities (limited evidence on TB)	Reduced muscle mass and strength of peripheral muscles. Lower muscle weakness with risk for falls. Impaired activities of daily living involving the upper extremities (including dressing, bathing, and household tasks)[11]	• Free weights (dumbbells and ankle-brace) • 20–30 min 2–5 times/week for 4–8 weeks • 2–3 set of 6–12 repetitions • Intensity set to 80% of maximal voluntary contraction and/or adjusted on muscles fatigue • In or out-patients or tele-monitoring • Suggest maintenance programme	• Free weights (dumbbells and ankle-brace) • 20–30 min 2–5 times/week for 4–8 weeks • 2–3 set of 6–12 repetitions • Intensity set according to perceived muscles fatigue • Out-patients or home setting • Suggest maintenance programme
Inspiratory muscle training (limited evidence on TB)	Impaired respiratory muscle function, altered respiratory mechanics, decreased chest wall compliance or pulmonary hyperinflation[100]	• Load threshold devices, seated and using a nose clip • Interval training: 10 exercises followed by 10 seconds break between each. • 15–20 min 2–5 times/week for 4–8 weeks • Loads from 30% to 80% of maximal inspiratory pressure	Not applicable
Airway clearance techniques	Difficult to remove secretions or mucous plugs Frequent bronchial exacerbations ($\geq$2/year) Concomitant diagnosis of bronchiectasis[101]	• Choose the technique suitable for the subject among those available, based on respiratory capacity, mucus rheology, collaboration and patient preferences • 15–30 min one or more times/day • Choose the duration of treatment based on chronic (long term) or acute problem (short term) • Suggest maintenance programme when needed	• Choose the technique suitable for the subject among those available, based on respiratory capacity, mucus rheology, collaboration and patient preferences • 15–30 min one or more times/day choose the duration of treatment based on chronic (long term) or acute problem (short term) • Suggest maintenance programme when needed
Long-term oxygen therapy (limited evidence on TB)	Resting hypoxaemia despite stable condition and optimal medical therapy (partial pressure of oxygen $<$7.3 kPa ($<$55 mmHg) or $\leq$8 kPa ($\leq$60 mmHg) with evidence of peripheral oedema, polycythaemia (haematocrit $\geq$55%) or pulmonary hypertension)[102,103]	• Titrate oxygen flow that maintain oxygen saturation $>$92–93% • Long-term oxygen therapy should be initiated on a flow rate of 1 L/min and titrated up in 1 L/min increments until oxygen saturation $>$90%. An arterial blood gas analysis should then be performed to confirm that a target partial pressure of oxygen $\geq$8 kPa (60 mm Hg) at rest has been achieved • Ambulatory and nocturnal oximetry may be performed to allow more accurate flow rates to be ordered for exercise and sleep, respectively during rest, sleep and exertion • Provide formal education to patients referred to home • Schedule periodic re-assessment at 3 months	• Titrate oxygen flow that maintain oxygen saturation $>$92–93% • Long term oxygen therapy should be initiated on a flow rate of 1 L/min and titrated up in 1 L/min increments until oxygen saturation $>$90% at rest has been achieved • Non-hypercapnic patients initiated on long term oxygen therapy should increase their flow rate by 1 L/min during sleep in the absence of any contraindications • Ambulatory oximetry may be performed to allow more accurate flow rates to be ordered for exercise • Provide formal education to patients referred to home • Schedule periodic re-assessment at 3 months

Table 3 (*continued*)

Components	Indication	Methods: Interventions	Methods: Adaption to special setting and situations
Long-term nocturnal non-invasive mechanical ventilation (limited evidence on TB)	Chronic stable hypercapnia (partial pressure of carbon dioxide >6–8 kPa (45–60 mmHg)), despite optimal medical therapy Non-invasive ventilation could be applied during aerobic training in case of severe breathlessness or reduced exercise resistance[91,104]	• Not initiating long-term non-invasive ventilation during admission for acute on-chronic hypercapnic respiratory failure, favouring reassessment at 2–4 weeks after resolution • Titrate non-invasive ventilation setting • Titrate mask • Plan education • Consider non-invasive ventilation during exercise • Schedule an educational meeting and verifies the ability of the subject and/or a caregiver to manage the non-invasive ventilation at home	Probably not applicable
Nutritional support	Malnutrition (body mass index <16 kg/m^2 or body mass index <17 kg/m^2 in patients with TB-HIV, MDR-TB, or pregnant and lactating mothers)[105–107]	• Nutritional assessment • Tailored treatment from foods and medical supplements • Need for financial incentives, and transportation access should be evaluated	• Nutritional assessment • Tailored treatment from foods and medical supplements • Need for financial incentives, and transportation access should be evaluated
Psychological support	Social isolation, depression and anxiety. Impaired health status and/or quality of life despite optimal pharmacological treatment. Low adherence to medical treatment[108,109]	• Psychological assessment • Psychological support • Consider self-help group	• Psychological assessment • Psychological support • Consider self-help group

MDR-TB = multidrug-resistant TB.

Table 4 Standard 4: Evaluation of pulmonary rehabilitation effectiveness

Outcomes		Type of measure: Essential and conditional examinations/investigations	Type of measure: Adaption to special setting and situations
Functional	Lung function	• Spirometry (FEV_1, FVC, FEV_1/FVC) • Plethysmography	• Spirometry (FEV_1, FVC, FEV_1/FVC)
	Gas transfer	• PaO_2, • $PaCO_2$ • Pulse oximetry (SpO_2, % desaturation) • DLCO, KCO	• Pulse oximetry (SpO_2, % desaturation)
	Exercise capacity	• 6MWT • VO_{2max} • ISWT • 5STS	• 6MWT • 5STS
TB-specific	Health-related quality of life	• EUROHIS-QOL 8 • SGRQ • WHOQOL-BREF • Paediatric: EQ-5D-Y and TANDI	• EUROHIS-QOL 8 • SGRQ • WHOQOL-BREF • paediatric: EQ-5D-Y and TANDI
	Self-reported symptoms	• mMRC • VAS • Modified Borg	• mMRC • VAS • Modified Borg
Generic	Acute infectious exacerbations (e.g., in bronchiectasis) requiring antibiotic and/or steroid treatment	Number of episodes	Number of episodes
	Hospitalisation	Number of episodes/hospital days	Number of episodes/hospital days
	Mortality (see Standard 6)	Number of deaths	Number of deaths

FEV_1 = forced expiratory volume in the first second; FVC = forced vital capacity; PaO_2 = partial pressure of arterial oxygen; $PaCO_2$ = partial pressure of arterial carbon dioxide; SpO_2 = peripheral capillary oxygen saturation; DLCO = diffusing capacity of the lungs for carbon monoxide; KCO = carbon monoxide transfer coefficient; 6MWT =six-minute walking test; ISWT = incremental shuttle walk test; 5STS = 5 repetitions of sit to stand test; VO_{2max} = maximal oxygen consumption; EUROHIS-QOL = EUROHIS-QOL = European Health Interview Survey-Quality of Life; SGRQ = St George's Respiratory Questionnaire; WHOQOL-BREF = abbreviated World Health Organization Quality of Life; TANDI = Toddler and Infant; mMRC = modified Medical Research Council; VAS = Visual Analogue Scale.

Table 5 Recommended examinations during anti-TB treatment and post-treatment follow-up

Time point/ assessment	M0*	M2/3*†	EOT*	M3† after EOT	M6‡ after EOT	M12¶ after EOT	Rationale	Comments
Microbiological examination of sputum (culture, microscopy or Xpert/NAAT)	x	x	x	(x)	(x)	(x)	Microbiological status before treatment initiation Monitoring treatment response and recurrent TB Determination of (microbiological) TB treatment outcome	Integrated in WHO or NTP guidelines
Clinical examination, including BMI	x	(x)	x	x	x	x	Identification of (potential) permanent TB sequelae and adverse effects of TB treatment Establish status quo at EOT to observe trend over time	Suggested use of a checklist to monitor for adverse drug events
Respiratory history and status of comorbidities (HIV infection, diabetes mellitus, COPD, CVD, nutrition status, cigarette smoking)	x		x	(x)	x	x	Identification and evaluation of potential risk factors that may have an influence on the prognosis and the management of PTLD Planning for interventions and education program Observing trend over time	Depending on the setting this should also include history such as vaccination status, exposure to silica and biomass fuel, investigations such as serology for hepatitis B/C, Sars-CoV-2, aspergillosis, nutritional status associated conditions such as anaemia
Chest radiography	x		x		(x)		Establish dimension of (permanent) pulmonary destruction before and after TB treatment Status quo at EOT to compare with future chest X-rays, e.g., assessment of respiratory exacerbations or recurrent TB Presence of cavities may increase risk of TB relapse and more severe PTLD sequelae	If available, digital radiography should be performed due to advantages regarding expert analysis, remote reading, automated analysis and data storage
Spirometry/ (plethysmography)	pre-TB	(x)	x	x	x	x	Capture lung function results before TB treatment, where available Establish status quo at EOT to compare with future spirometry testing Identification of subjects for rehabilitation	ERS/ATS guidelines should be followed Adequate reference standards should be used for result interpretation Appropriate equipment, including maintenance of equipment needed Body-plethysmography, only for research purpose or in specific patients and settings
Computed tomography			(x)		(x)		Allows a more refined investigation of pulmonary structures and pathologies, e.g., bronchiectasis, fibrosis, aspergillosis of the lung Presence of cavities may increase risk of TB relapse and more severe PTLD sequelae	Recommended in symptomatic patients or in patients with TB-related abnormalities, which cannot be well investigated on chest radiography
6MWT	pre-TB		x	x	x	x	Establish physical exercise capacity (before –if available- and) after TB treatment Status quo at EOT to compare with future 6MWTs Identification of subjects, who may potentially benefit from rehabilitation	Very useful to observe trend over time May be additionally indicated after recovery of exacerbated patients Validated for other respiratory conditions including prognosis evaluation

Table 5 (*continued*)

Time point/ assessment	M0*	M2/3*†	EOT*	M3† after EOT	M6‡ after EOT	M12¶ after EOT	Rationale	Comments
SpO_2	(x)		x	x	x	x	Severity staging of respiratory failure Evaluation of nocturnal and/or exercise-associated oxygen desaturation Information for the indication of LTOT May be helpful for evaluation of patients with acute exacerbations	Integrated part of 6MWT Less accurate than BGA
BGA			(x)		(x)	(x)	Diagnosis and severity staging of respiratory failure Information for the indication of LTOT	Only for research purpose or in specific patients and settings More accurate and provides more information compared to SpO_2 Metabolic disturbance diagnosis Appropriate equipment, including maintenance of equipment needed
DLCO, KCO			(x)		(x)	(x)	To assess CO-diffusion capacity and identify the underlying cause of impaired lung gas-exchange	Only for research purpose or in specific patients and settings Useful for consideration of pulmonary hypertension and other causes of dyspnoea Appropriate equipment, including maintenance of equipment needed
Tidal breathing techniques (oscillometry/ MBW)	(x)	(x)	(x)	(x)	(x)	(x)	Assessment of small airways and of ventilation heterogeneity seen in complex structural lung disease	Only for research purpose or in specific patients and settings Oscillometry easy to perform in children and other patients, who cannot perform spirometry
QoL questionnaire (including dyspnoea score)	(x)	(x)	x	x	x	x	Establish the severity of respiratory symptoms and quality of life impairment after TB treatment Status quo to compare with future evaluations Identification of subjects with potential benefit from rehabilitation	Depending on the context and educational level, validated scales and questionnaires suitable for the patient should be chosen
ECG			(x)		(x)	(x)	Supports diagnosis of secondary cardiac damage due to chronic lung diseases, including PTLD Differential diagnosis between primary and secondary cardiac diseases	Only for research purpose or in specific patients and settings
Cardiac-ultrasound (echo)			(x)		(x)	(x)	Allows diagnosis of secondary conditions due to TB or PTLD such as constrictive pericarditis, pulmonary hypertension, right heart failure Differential diagnosis between primary and secondary cardiac disease	Only for research purpose or in specific patients and settings Could be complemented by measurement of NT-pro-BNP to rule out heart failure

* x = all centres; (x) = research-oriented centres, specific settings or patients (depending on comorbidities, symptoms, exacerbations or abnormal findings in other tests).
† Optional evaluation during TB treatment/at the end of the intensive treatment phase; depending on patients' symptoms (e.g., re-evaluation of TB- or PTLD-diagnosis, diagnosing special conditions such as IRIS or co-infections such as Sars-CoV-2) or specific situations and settings.
‡ Follow-up visits at M3 and M6 after EOT may overlap with pulmonary rehabilitation activities and assessments.
¶ Further follow-up of patients with (high risk for) PTLD; 6–12 monthly follow-up visits, depending on clinical patterns, diseases severity, disease dynamics and comorbidities.
NAAT = nucleic acids amplification test; M = month; EOT = end of treatment for TB; NTP = National Tuberculosis Programme; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; QoL = quality of life; PTLD = post-TB lung disease; ERS = European Respiratory Society; ATS = American Thoracic Society; 6MWT = 6 minutes walking test; SpO_2 = oxygen saturation using pulse oximetry; LTOT = long-term oxygen therapy; BGA = blood gases analysis; DLCO = diffusing capacity of the lung for carbon monoxide; KCO = carbon monoxide transfer coefficient; MBW = multiple breath washout; ECG = electrocardiogram; NT-pro-BNP-N = terminal pro brain natriuretic peptide.

Health education is an essential part of PR.[87] The multidisciplinary education component includes information on PTB and most frequent respiratory comorbidities. This generally covers lung anatomy, physiology of various lung impairments, exercise physiology, benefits and methods of daily training, nutrition, drug therapy, oxygen therapy, how to cope with exacerbations and how to manage daily life.[88] Health education should also involve patients and their families. This is especially important for children, where education about TB prevention, smoking, cough etiquette and other topics (see Table 6) is recommended for the whole household.

Educating patients to self-manage sputum clearance contributes to reducing the frequency of exacerbations and the unnecessary use of antibiotics (thus preventing antibiotic resistance development and spread). In addition, WHO recommends integrating early and effective smoking cessation measures and risks posed by alcohol abuse, starting at the primary health care level, into TB control plans.[115,116] Health education or counselling should be organised according to international guidelines.[117] Importantly, health education sessions should be age-specific, gender-sensitive and delivered in the patient's own language.[41,42] Recommendations to deliver an effective educational session are summarised in Table 6.

Table 6 Standard 5: Summary of the components of the counselling/health education session

Components:
- Structured and comprehensive educational programmes are an integral and essential component of the management of PTLD and pulmonary rehabilitation
- Educational programmes should be age-specific, gender-sensitive, delivered in the local language and extended to families/households
- Education should be delivered by professionals who are competent in the relevant subject areas and trained to deliver educational sessions
- Educational materials and technological support used to deliver them needs to be evaluated in the setting-specific context

Recommended topics:
- Basic principles of TB: epidemiology, clinical aspects and transmission (reinforcing what is ideally provided at diagnosis)
- Importance of treatment (and treatment adherence/retention in care) to stop transmission, protect contacts and prevent relapses
- Simple concepts of infection control and safety procedures
- Advantages/importance of smoking cessation and risk of comorbidities (e.g., HIV co-infection, diabetes, etc.) in household/families
- Importance of physical activity and exercise to improve quality of life
- Maintaining results achieved with pulmonary rehabilitation (follow-up plan)
- Ensuring adequate nutrition
- Importance of adhering to medical prescriptions in terms of management of comorbidities and vaccinations
- Recognising deterioration of clinical conditions and what actions to undertake to prevent relapse
- Achieving an optimal healthy life style

PTLD = post-TB lung disease.

STANDARD 6 (PUBLIC HEALTH)

Each change in outcome for a patient (cured or treatment completed as per WHO guidelines) occurring during or after PR should be promptly notified to public health services and be included in the TB register. If the TB register/surveillance database allows, for research purposes the results of the PR programme should be recorded and updated over time. Patients with permanent sequelae and disability need to be supported by social protection schemes whenever possible, according to the legal framework in place.

Standard 6 is the only public health standard included in this clinically oriented document. The WHO has introduced outcomes definitions, which have recently been revised.[46] These definitions are used by TB programmes for monitoring and evaluation purposes, e.g., to allow them to measure rapidly the proportion of patients achieving treatment success (cure, if evidence of bacteriological negativity in a previously positive patient exists, otherwise treatment completion) against those with negative outcomes (e.g., treatment failure, lost to follow-up, or died).[118–121] When revising the definition of cure, the WHO recommended, when possible, to continue the follow-up of patients for a period of 6 months or 1 year.[46] This was based on evidence that relapses or re-infections can occur, and introduced the concept of 'sustained cure'. Patients undergoing PR allows for follow-up to occur, as they remain in care after completing their TB treatment.

Standard 6 calls for the need to update the TB register if any change occurs in the final outcome (cure or treatment completion), e.g., if the patient develops relapse (or recurrence with evidence of re-infection), or if death occurs. If the TB programme's surveillance system/TB register allows, information that the patient has been evaluated for PTLD should also be recorded. Together with this, if there was an indication for PR implementation and evaluation, the outcome could be recorded. These inclusions will improve the information globally available on PTLD and contribute to its better management. If the surveillance system/TB register does not allow for this, the information could be collected at the clinical centre level and periodically collected/evaluated for research purposes. Communication between the TB register and the clinical staff is encouraged.

An additional important element of Standard 6 is the importance of prioritising patients with severe PTLD to ensure access to social protection schemes, based on existing legislation (but which we recommend should be revised to capture this concept). This element is fully in line with Pillar 2 of the WHO End TB Strategy.[122,123]

Table 7 Research priorities

	Research priority	Type of studies
1)	To describe the frequency and severity of PTLD in different populations and subgroups of TB patients over time since the completion of TB treatment, including in children and adolescents	Cross-sectional studies, cohort studies
2)	To establish risk factors for severe PTLD and associated poor health outcomes, including elevated mortality	Cohort studies (case-control studies)
3)	To quantify the health and economic impact of PTLD at the individual and population level, including the impact of managing PTLD on health systems	Health economic/mathematical modelling studies
4)	To identify feasible, accurate and cost-effective tools to evaluate patients at the end of TB treatment for their risk of PTLD and subsequent poor health outcomes (Standard 1)	Diagnostic accuracy studies, diagnostic randomised-controlled trials
5)	To develop optimal approaches and algorithms to diagnose and manage PTLD, and to discriminate between PTLD and recurrent TB (Standards 1, 2)	Diagnostic accuracy studies, diagnostic randomised-controlled trials
6)	To identify effective and cost-effective strategies to prevent PTLD during anti-TB treatment, including, for example, adjuvant therapies and interventions to reduce concomitant risk factors for poor lung health outcomes (e.g., smoking cessation programmes)	Randomised-controlled trials
7)	To identify effective and cost-effective strategies to deliver pulmonary rehabilitation in specific sub-groups (using standard measures of minimum clinically important difference), including individual patient follow-up in different settings and populations (Standards 2–5)	Randomised-controlled trials
8)	To investigate the role of patient education programmes in improving long-term health outcomes post-TB (Standard 5)	Randomised-controlled trials
9)	To investigate the role of social protection and support programmes in improving health outcomes and quality of life among former TB patients (Standard 6)	Randomised-controlled trials
10)	To identify a set of standard indicators for the surveillance of PTLD that are feasible to implement within national TB programmes (Standard 6)	Operational research studies

PTLD = post-TB lung disease.

PRIORITIES FOR FUTURE RESEARCH

There is a need for additional research on the epidemiology, assessment and management of PTLD in adults and children to guide the development of future standards and guidelines. To enable research in the forthcoming years, political commitment and appropriate funding mechanisms will be essential. Key research priorities are highlighted in Table 7.

CONCLUSION

There is a need for continued care for TB patients who successfully complete TB treatment but continue to suffer from PTLD.[1,2,4] This document represents the views of a large body of experts who have reached consensus on clinical standards for the assessment and management of PTLD and, as necessary, the implementation of PR.

The document also presents a set of research priorities to improve our understanding of the measures that will prove to be most effective (and cost-effective) to prevent, detect and treat PTLD. Because the evidence currently available is modest, this document will be revised periodically to guide clinicians, TB programme managers and public health officers towards evidence-based planning and implementation of adequate measures to assess and manage PTLD.

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RÉSUMÉ

CONTEXTE : Un nombre croissant de données probantes suggèrent que la maladie pulmonaire post-TB (PTLD) est à l'origine d'une morbidité et d'une mortalité significatives. L'objectif de ces normes cliniques est de fournir des conseils sur l'évaluation et la prise en charge de la PTLD, ainsi que sur la mise en place de la rééducation pulmonaire (PR).

MÉTHODES : Un panel de 67 experts internationaux en matière de soins antituberculeux et de PR a été identifié ; 62 experts ont participé à un processus Delphi. Une échelle de Likert en cinq points a été utilisée pour évaluer les idées initiales de normes et, après plusieurs révisions, le document a été approuvé (par consensus).

RÉSULTATS : Cinq normes cliniques ont été définies : Norme 1, pour évaluer les patients à la fin de leur traitement antituberculeux (avec adaptation pour les enfants et à certains cadres particuliers/certaines situations particulières) ; Norme 2, pour identifier les patients présentant des séquelles et une PTLD ; Norme 3, pour identifier les personnes pour qui une PR et d'autres interventions seraient bénéfiques ; Norme 4, pour prendre en charge la PR et évaluer son efficacité ; et Norme 5, pour mener des campagnes d'éducation et fournir des conseils. La Norme 6 présente les priorités de santé publique en matière de recherche.

CONCLUSION : Il s'agit du premier ensemble de normes cliniques pour la PTLD fondées sur un consensus. Notre objectif est d'améliorer les soins et la qualité de vie des patients en aidant les cliniciens, les responsables de programme et les fonctionnaires de la santé publique à organiser et mettre en place des mesures adaptées à l'évaluation et à la prise en charge la PTLD.