Developing core outcome sets for clinical research and guideline development – qualitative systematic reviews to increase the volume, depth and diversity of patient perspectives included.

Tuberculosis: a case study.

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List of abbreviations

ASSIA
Applied Social Sciences Index and Abstracts

CASP
Critical Appraisal Skills Programme

CERQual
Confidence in the Evidence from Reviews of Qualitative Research

CFU
Colony-forming unit

COMET
Core Outcome Measures in Effectiveness Trials

COS
Core outcome set

DOT
Directly observed therapy

DOTS
Directly observed therapy short-course

ENTREQ
Enhancing transparency in reporting the synthesis of qualitative research

GRADE
Grading of Recommendations Assessment, Development and Evaluation

HIV
Human immunodeficiency virus

MDR-TB
Multidrug-resistant tuberculosis

MeSH
Medical Subject Headings

NICE
National Institute for Health and Care Excellence

OMERACT
Outcome Measures in Rheumatology

QARI
Qualitative Assessment and Review Instrument

RA
Rheumatoid arthritis

RCT
Randomised controlled trial

SPICE
Setting, Perspective, Intervention, Comparison, Evaluation

TB
Tuberculosis

WHO
World Health Organization

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Developing core outcome sets (COS) for clinical research and guideline development – qualitative systematic reviews to increase the volume, depth and diversity of patient perspectives included.

Tuberculosis: a case study.

Abstract

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Background. Patient involvement is a core value of contemporary healthcare, and an emerging component of core outcome set (COS) methodology. This research pilots the use of qualitative systematic reviews to increase the volume, depth and diversity of patient perspectives included in COS development, specifically for a COS for tuberculosis (TB). A COS for TB will ensure that outcomes across trials are consistent, free from selection bias and relevant to patients, clinicians and policy-makers.

Methods. ASSIA, CINAHL, Embase, MEDLINE and PsycINFO were searched for qualitative studies exploring patient perspectives on tuberculosis and its management. Studies were appraised using the CASP checklist and thematic synthesis utilised to identify treatment outcomes of potential importance to patients. The overall confidence in the review findings was assessed using the CERQual approach.

The outcomes identified as important were compared against those used in planned and existing Cochrane reviews, and against those used in the new NICE guidance on TB, to investigate the need for future work to consider more patient-centred outcomes.

In order to assess the potential value of adding qualitative evidence synthesis into COS methodology, the volume and diversity of patient perspectives incorporated in the review were compared against those included in published COS literature that utilised qualitative research in patient populations (without synthesis).

Findings. Improvement in the signs and symptoms of disease, mortality and survival, treatment failure, success and cure, the adverse effects of treatment, and the impact of treatment on the patient's ability to function were identified as important to patients. The confidence in these review findings ranged from low to very low.

These outcomes were not consistently reported in Cochrane reviews, nor in the primary studies included in these reviews. The outcomes were addressed to a greater extent in the reviews underpinning the updated NICE guidance. The impact of treatment on the patient's ability to function was not considered by any review.

The use of qualitative systematic reviews improved the volume and diversity – the geographical coverage, the range of age groups and the balance of men and women – of patients' perspectives available when compared to the published COS literature.

Conclusions. The outcomes identified in the review should be considered within the development of a core outcome set for TB, but also by those planning future trials into the effectiveness of antituberculosis treatments and future qualitative research into outcome prioritisation for TB trials. The research has provided a tentative rationale for the use of qualitative systematic reviews more widely within COS development. However, these benefits should be considered in light of a trade-off against the significant time and resource required in conducting a qualitative systematic review. More extensive use of these methods should perhaps wait until there is a greater volume of directly relevant qualitative research available.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Copyright statement

The author

The author of this research has previously received a BSc in Biomedical Science from Kings College London, and an MSc in Biomedicine, Bioscience and Society from the London School of Economics & Political Science. She is currently employed at the National Institute for Health and Care Excellence as a systematic reviewer and developer of clinical guidelines.

Introduction

This research will explore the use of qualitative systematic reviews to increase the volume, depth and diversity of patient perspectives included in core outcome set (COS) development, applying this novel approach to a COS for tuberculosis. The review findings will be compared against existing literature to determine their potential value for driving future research, both in terms of the outcomes used in clinical trials for TB treatment and the methodology used for COS development.

A core outcome set for tuberculosis?

This chapter will explore the need for developing a COS for tuberculosis, and discuss the need for COS in clinical effectiveness research more generally.

CORE OUTCOME SETS: AN INTRODUCTION

> *"Outcomes can reflect various effects of an intervention. They may directly measure a definitive clinical change, such as death or hospital admission. Surrogate outcomes, which are sometimes used in lieu of a definitive clinical outcome, aim to capture the effects of an intervention without having to wait for the clinical change to actually occur. In other words, they are proximal to the clinical outcome on the disease pathway, so a change can be detected sooner. They may be a measure of intermediate health status, which may be used to predict future health status." (Sinha* et al.*, 2008)*

Clinical trials are conducted to evaluate the effectiveness of interventions in the prevention, control or management of a particular condition. This is achieved through the measurement of a number of 'outcomes' in a population with the condition of interest in response to the use of the intervention(s) of interest. These measures of effectiveness reflect the potential benefits and harms of an intervention – in terms of, for example, changes in a patient's risk of morbidity or mortality, in their physiological or biochemical status, or in terms of changes in their behaviour in response to receiving that intervention.

> *"Clinical trials are only as credible as their endpoints." (Tugwell & Boers, 1993a)*

As the instruments by which clinical trials collect and report their effectiveness data and, in so doing, the instruments by which they fulfil their remit, outcomes are central to the validity, credibility and utility of a trial.

> *"The selection of inappropriate outcomes can lead to wasted resources or misleading information that overestimates, underestimates, or completely misses the potential benefits of an intervention." (Sinha* et al.*, 2008)*

Despite this, there is an increasing recognition that many trials do not give outcome selection the robust consideration or rigour required. The core outcome set – "an agreed standardised set of outcomes … which should be measured and reported in all trials for a specific clinical area"

(Williamson *et al*., 2012a) – has been proposed as a tool to assist those conducting clinical trials in selecting, measuring and reporting data for the most appropriate outcomes.

Firstly, outcomes selected to evaluate an intervention's effectiveness need to be relevant to those for whom the generated data is intended as the basis for decision-making – that is, patients and clinicians, as well as policymakers and those involved in or planning related research. Conducting clinical trials requires considerable resources, in terms of the costs, staffing, the burden and risks placed upon participants, the time required to plan and conduct a trial, the resources required to subsequently analyse the data produced, and so on. Subsequently,

> *"Measuring outcomes that will not change healthcare decisions leads to a waste of resources and a failure to capitalise on the potential power of research to improve health care and health … If researchers want their work to resolve uncertainty and improve decision making in health care, they need to ensure that the outcomes they include are relevant to health service users (consumers) and other people making choices about health care." (Williamson & Clarke, 2012)*

COS are widely touted by their proponents as having the potential to minimise such squandering of valuable resources and as an opportunity to improve the usefulness and relevance of clinical trial data to clinical decision-making (for example, Williamson *et al*., 2012b; Kirkham, *et al*., 2013; Payne, *et al*., 2007; Sinha, *et al*., 2008; Sinha, *et al*., 2012; Smaïl-Faugeron, *et al.,* 2013; Tugwell, *et al*., 2007; Turk, *et al.*, 003). This is primarily because a core component of COS methodology involves consultation with patients, clinicians and other key stakeholders about their information needs.

The usefulness of a set of outcomes demonstrated to be those most important to patients goes beyond the design of clinical trials. With a growing emphasis upon patient-centred healthcare in many parts of the world, COS developed with patient involvement will be valuable assets in the production of clinical guidelines and other forms of evidence-based healthcare policies. For example, in the methodological manual for the development of their clinical guidelines, the National Institute for Health & Care Excellence in the United Kingdom explicitly state that when selecting outcomes for review questions about interventions they will consider the question, "What is really important for people using services?" (2014). Likewise, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group[1] state that "guideline developers must, and authors of systematic reviews ideally will, specify all potential patient-important outcomes as the first step in their endeavour" (Guyatt, *et al*., 2011).

[1] "A group of health professionals, researchers, and guideline developers worldwide who, in 2000, began to work together to develop an optimal system of rating quality of evidence and determining strength of recommendations for clinical practice guidelines." (Guyatt, *et al*., 2010)

Standardised outcome sets developed with significant patient involvement will not only provide a valid framework for the development of clinical guidelines, but will reduce the public resources used in development by reducing the work required for the selection of appropriate patient-important outcomes.

> *"Meta-analyses frequently exclude a large number of trials because relevant outcomes are not reported" (Smaïl-Faugeron,* et al.*, 2013)*

In addition to supporting patient-centredness, COS would also benefit evidence-based clinical guidelines, and systematic reviews more generally, by increasing the consistency of the outcome data collected and reported across clinical trials. This will in turn facilitate the aggregation of data from multiple studies using meta-analytical techniques. Variations in the choice of outcome measures leads to considerable heterogeneity in the available evidence, and means that meta-analyses are often unable to include data from every relevant clinical trial.

For example, Williamson and Clarke (2012) note that the five most accessed Cochrane reviews of 2009 "all described the difficulties caused by inconsistencies in the outcomes reported in eligible trials". In a review of interventions for preventing obesity in children, the reviewers "did not undertake a meta-analysis of the effects of the interventions on prevalence of overweight or obesity [listed as a primary outcome] due to two factors: it was not reported in the majority of studies, and there was highly variable methods used for the classification of overweight and obesity" (Waters, *et al*., 2011). In a review of interventions for treating obesity in children, wide variations in the time points at which outcome data were reported prevented the inclusion of all studies in a number of the meta-analyses (Oude Luttikhuis, *et al*., 2009). In a review of interventions for preventing falls in older people living in the community, a number of trials met the reviewers' inclusion criteria "but did not include any data that could be included in these analyses" (Gillespie, *et al*., 2009), and none of the studies reported every outcome of interest. The other two reviews discussed by Williamson and Clarke reported similar issues relating to heterogeneity in outcome data (Gillespie, *et al*., 2003; Orozco, *et al*., 2008). In these reviews, the statistical power and precision of treatment effect estimates are likely to be significantly lower than might be the case if all relevant studies provided data that could be included in the analysis. Standardisation of outcomes is needed to combine data from different studies to allow evidence synthesis and comparison of data sets.

Examining data from 350 randomised trials for the treatment of rheumatoid arthritis, Kirkham and colleagues (2013) empirically demonstrated the benefits of developing a standardised set of outcomes and implementing it in subsequent clinical research. Rheumatoid arthritis was chosen because of the condition's long history in outcome development,

> *"In RA [rheumatoid arthritis], it has been common practice since the 1950s to use a selection of traditional measures to define the endpoints of most clinical trials, usually including measures based on the clinician's physical examination, global assessment, laboratory measurements and*

> *sometimes radiographs. However, during the 1980s, it became clearer to researchers that the measures chosen rarely included patient reported outcomes, were not comprehensive, some were insensitive to change, and others measured the same phenomenon and were thus redundant. Furthermore, it was notable that the choice of outcomes was variable between trials: for instance, clinical trials of patients with RA in the USA measured different outcomes to those conducted in Europe." (Kirkham,* et al*., 2013)*

The response to the noted deficiencies in the approach to outcome selection was 'OMERACT', or the Outcome Measures in Rheumatology, initiative. The group met for the first time in 1992, and produced the first COS for trials of symptom-modifying drugs in rheumatoid arthritis in 1994. A review of outcome selection in rheumatoid arthritis trials by Kirkham *et al*. (2013) found that, after the publication of this COS and its successive iterations, "marked increases were found in the measurement of the full set of RA core outcomes in pharmacologic interventions", with the authors concluding that

> *"The adoption of a COS has the potential to increase the consistency in outcomes measured across trials … and ensure that trials are more likely to measure appropriate outcomes … 60% to 70% of trialists conducting trials in RA are now measuring the RA COS. Of the trialists contacted, 90% said they would consider measuring the RA COS if they were to lead a new trial in RA." (Kirkham,* et al*., 2013)*

> *"Without a consensual and validated set of outcomes, clinical researchers may favour outcomes that enhance trial feasibility or results rather than clinician- or patient-important outcomes." (Smaïl-Faugeron,* et al*., 2013)*

The third major argument for the production and implementation of COS in clinical research is its potential for minimising the risk of outcome reporting bias in the evidence base. Selective reporting bias has been described as "the selection, on the basis of the results, of a subset of the analyses undertaken to be included in a study publication". (Williamson, *et al*., 2005) This bias might, for example, manifest through way in which the outcome data is parameterised for reporting: through the choice of outcome subscales, the threshold chosen for converting a continuous measure into a binary measure, or the time point reported when the same outcome was in fact recorded at a variety time points. Alternatively, selective reporting bias may apply to the preferential reporting of outcome data parameterised in other ways, for example by population subgroups or prognostic factor.

> *"Bias in reporting of clinical trials and selective publication can create false perceptions of drug efficacy and safety. There is evidence for selective reporting of favourable results and suppression of unfavourable data from publication, leading to inappropriate conclusions … Selection*

> *bias can affect not only the interpretation of the trial itself but also the interpretation of subsequent systematic reviews or overviews, producing inaccurate summaries of research and misrepresentation of toxicity. Reporting of harms may be viewed as discrediting the reporting of benefits." (Vera-Badillo,* et al*., 2013)*

A significant amount of empirical research has demonstrated the prevalence of selective outcome reporting in the published literature. For example, one review of 519 randomised controlled trials demonstrated that, "on average, over 20% of the outcomes measured in parallel group trials were incompletely reported" (Chan and Altman, 2005). The reasons for not reporting outcomes were explored through a survey of the included studies' authors, and the most common explanations given were space constraints in the reports, a lack of statistical significance or a lack of clinical importance. Furthermore, a systematic review of 16 papers that compared study protocols and published reports has reported that "40–62% of studies had at least one primary outcome that was changed, introduced, or omitted" (Dwan, *et al*., 2008). It was also noted that "12 of the included empirical studies demonstrate consistent evidence of an association between positive or statistically significant results and publication." For example, one of the included studies noted that, "statistically significant outcomes had more than a 2-fold greater odds of being fully reported compared with nonsignificant outcomes" (Chan, *et al*., 2004).

Where authors have given a 'lack of clinical significance' as a reason for not fully reporting an outcome or outcomes, the question arises as to why this outcome was measured in the first place. Perhaps insufficient consideration was given to outcome selection in the planning phase of the trial, or perhaps the outcome did not yield data considered sufficiently noteworthy for publication, or perhaps the data was at odds with the expected or desired result. Although potentially less 'sensational' than a significant difference in treatment effects, a demonstration of no difference in effect can be equally useful to clinical decision-making. Additionally, as with the censoring of data because of its divergence from an expected or desired direction (selective reporting bias), it means that patients and clinicians are not in possession of all relevant information. This is particularly concerning where the data would be used to make decisions regarding the use of interventions that may affect the risk of morbidity and mortality in patients. COS, as a standardised set of outcomes considered important by patients and clinicians that should be measured and reported in all trials for a specific clinical area, would help to minimise outcome reporting bias and these associated issues.

The core outcome set has been proposed as a tool to assist those conducting clinical trials in ensuring the relevance of the outcomes they measure to patients and clinicians, in enhancing the consistency of outcomes reported across trials, and thus the power and precision of evidence synthesis through systematic review and meta-analysis, and as a tool for reducing

the bias associated with selective outcome reporting. As stated by members of the COMET (Core Outcome Measures in Effectiveness Trials) Initiative[2],

> *"These sets do not imply that outcomes in a particular trial should be restricted to those in the COS. Rather, there is an expectation that the core outcomes will always be collected and reported, and that researchers will continue to explore other outcomes. In most trials, the primary outcome would be expected to be one of those contained in the COS. If a COS is not implemented in a particular trial, the researchers should explain their decision in the trial protocol and subsequent report. Similarly, if the primary outcome for a particular trial is not within the COS, then the relevance and importance of the chosen outcome should be explained." (Williamson* et al*., 2012a)*

CASE STUDY: TUBERCULOSIS

This work will explore the emerging methodology for the development of COS through the design of a COS for tuberculosis. According to the COMET Initiative's database of published and ongoing work in COS development (available at: http://www.comet-initiative.org/studies/search; accessed: 10 December 2015), work has now commenced on a set of standardised, agreed outcomes for effectiveness trials of interventions for the treatment and management of tuberculosis. Thus far, a review of outcomes published in phase II studies of newly-diagnosed pulmonary tuberculosis has been published *(Bonnet and Davies, 2015)* and further work with stakeholders (clinical experts, consumers (patients), and service providers) is ongoing (Zhang *et al*., no date).

Tuberculosis (TB) is a granulomatous inflammatory disease caused by strains of mycobacteria belonging to the *Mycobacterium tuberculosis* complex. It is acquired through inhalation of aerosolised bacilli from the coughs or other respiratory fluids of an infected person. The most common form of TB is the asymptomatic and non-infectious latent infection, but in a proportion of patients the latent infection will overwhelm the immune system and advance to active disease. This proportion is relatively small, occurring in 5% to 10% of cases (Knechel, 2009), though some people are at a much greater risk of progression, including people with human immunodeficiency virus (HIV) and other immunocompromised individuals. Given that infection generally occurs through inhalation, the disease most commonly attacks the lungs

[2] An initiative "bring[ing] together people interested in the development and application of agreed standardised sets of outcomes" *(COMET Initiative, no date)* and a major advocate of COS.

('pulmonary TB'), although it can also spread to any part of the body through the lymph or circulatory systems ('extrapulmonary TB').

Once active, multiplication of the bacilli, caseous necrosis and tissue-damaging hypersensitivity in the lung and surrounding lymph nodes lead to the formation of lesions and cavities (Grossett, 2003), as well as fibrosis, calcification and scarring. These, in turn, are associated with the characteristic cough that eventually develops in nearly all patients, as well as blood in the sputum (or 'haemoptysis'). Other manifestations of the disease include chest pain, lack of appetite, weight loss, fatigue, malaise and fever accompanied by chills and night sweats (Knechel, 2009).

With appropriate multidrug treatment regimens of sufficient duration, tuberculosis is a curable disease and has been since the 1950s. However, left untreated the disease has a 10-year case fatality rate of 70% in people who are HIV-negative and 83% in people coinfected with HIV (Tiemersma *et al*., 2011). Even where implemented, the lengthy regimens (a minimum of 6 months) with their complex cocktails of drugs and unpleasant side effects can be difficult to adhere to, and long-term treatment success and a return to full physical functioning are not guaranteed. For example, pulmonary tuberculosis, even amongst those who are cured, can lead to significantly reduced lung capacity, breathing difficulties and even lung failure, and can therefore have a significant impact on quality of life.

In addition to differentiation by latency and by site, tuberculosis also manifests itself along a spectrum of drug susceptibility: bacilli may be responsive to all antituberculosis drugs, or they may be resistant to one or more. Resistance is a product of misuse or mismanagement of antituberculosis chemotherapy leading to levels of drugs that are insufficient to eradicate all infection from the body. Resistance emerges when some or all of the remaining bacilli, which proliferate to establish a new infection, have mutated to exhibit resistance to one or more drug.

Drug resistant TB requires much longer regimens, and sometimes a greater number of different drugs which are often more expensive and associated with greater toxicity and side effects. For example, the World Health Organisation recommends that people with multidrug resistant TB (MDR-TB) – defined as resistance to the two first-line (and most powerful) antituberculosis drugs, rifampicin and isoniazid (World Health Organisation, 2013) – should receive treatment for at least 20 months, and that the regimen should, in addition to first-line drugs, include at least four second-line drugs (World Health Organisation, 2011). Not only does this place a much greater burden upon the patient, but the treatment of resistant strains of TB is not associated with a high rate of success. For example, the proportion of MDR-TB patients who successfully completed treatment, defined as the sum of those considered to be cured and those considered to have completed treatment as recommended but not to have been cured, in 2012 was just 50% (World Health Organisation, 2015). 16% died.

Further to the physical effects, the burden of TB also manifests in a number of social aspects. Although public understanding and discourse surrounding the condition has improved in recent years, a significant level of ignorance and stigma persists (see, for example: Baral, *et al*., 2007; Dodor and Kelly, 2009; Jittimanee, *et al*., 2009; Macq, *et al*., 2008; Nnoaham, *et al*., 2006). This represents a substantial barrier to connecting patients with health services, and affected individuals or groups can suffer discrimination or social isolation.

Additionally, many TB cases occur in regions or groups already considered to be 'vulnerable' or 'hard-to-reach'. At the regional level, the countries with the highest incidence of tuberculosis – India, China, Myanmar, the Democratic Republic of Congo, Ethiopia, Philippines, Bangladesh, Pakistan, Indonesia and South Africa (World Health Organisation, 2015) – all score poorly on one or more indicator for human development, such as poverty, health, education, social integration or gender inequality (United Nations Development Programme, 2015). Even in low-incidence countries, vulnerable or hard-to-reach groups are significantly affected. In the UK, for example, Public Health England report that in 2013 10% of cases had one or more social risk factors, which include a history of homelessness, imprisonment and substance misuse (Public Health England, 2014). This rose to 17% amongst those born in the UK. Additionally, nearly half (44%) of the cases reported in adults in the UK in 2013 were unemployed (Public Health England, 2014). Although it is unclear from the data if these patients were unemployed on diagnosis with TB or if unemployment occurred subsequent to their diagnosis, it illustrates another socioenconomic phenomenon often associated with the disease: the physical and social effects discussed above can impact significantly upon a person's ability to obtain employment or to maintain it, creating significant financial burdens on patients and their families.

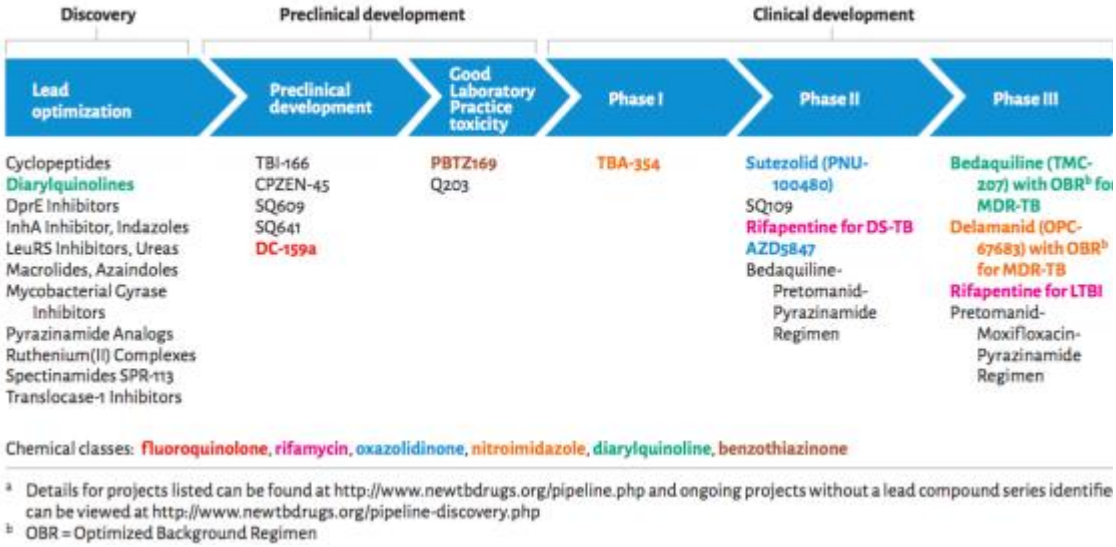
Despite some success in reducing TB incidence since declaring it a global public health emergency in 1993, the World Health Organisation (2015) estimates that in 2014 there were still approximately 9.6 million cases of tuberculosis and 1.5 million tuberculosis-related deaths worldwide. Efforts to reduce the incidence and impact of this disease have been hampered by numerous factors. These include the length and burden of current treatment regimens, the emergence of drug resistant strains of the disease, the spread of HIV, the high incidence among vulnerable and hard-to-reach groups, difficulties in achieving an early and accurate diagnosis, concerns over the longevity of protection provided by the Bacillus Calmette-Guérin (BCG) vaccine, and, until recently, the relatively small amount of new high-quality research that has been conducted to meet these challenges.

In response to these demands, however, new research is and has been ongoing. A significant amount of research has been conducted in recent years into new, rapid diagnostics for active tuberculosis and drug susceptibility testing, into new vaccines, into treatment regimens for latent tuberculosis, into service organisation, into case management and contact-tracing, and – particularly relevant to the focus of this research project – into new antituberculosis drugs and regimens for active disease.

"New drugs are required to shorten and simplify treatment, to improve the efficacy and tolerability of treatment for MDR-TB and to improve the treatment of TB among people living with HIV." (World Health Organisation, 2013)

At this time, there are 6 new or repurposed antituberculosis drugs undergoing Phase II and Phase III trials, 5 drugs in preclinical development and a further 11 classes of drug in discovery (see Figure 1 for more details) (World Health Organisation, 2015). Further to this, new regimens – in terms of shorter durations of treatment and previously unused combinations of drugs – are also being trialled. A COS would be invaluable in ensuring that these trials produce useful, consistent data that suffers from minimal outcome selection or reporting bias.

Figure 1. The development pipeline for new TB drugs, August 2015 (reproduced from World Health Organisation, 2015)



Although no COS currently exists for tuberculosis, the World Health Organisation has developed a reporting framework for epidemiological data collection. This framework consists of standard definitions for cases of TB and drug-resistant TB, including treatment outcome definitions, that should be used by national TB programmes in their monitoring of programme performance, allowing data to be compared internationally (World Health Organisation, 2013b). Outcomes for which the framework provides a definition and which may be relevant to the assessment of the effectiveness of interventions include: cure, treatment completion, treatment success, treatment failure and tuberculosis-related mortality.

Whilst these outcomes and their definitions could, to some extent, address issues relating inconsistencies in outcome reporting between trials, there are a number of reasons why they do not fully accomplish the objectives of a COS. Firstly, this set of outcomes was not developed for use in clinical effectiveness trials – as described above, they were developed for epidemiological data collection and programmatic monitoring. Outcomes for effectiveness trials need to be precisely defined, whereas the World Health Organisation outcomes are intentionally broad and flexible so as to accommodate the different diagnostics used in different countries.

Although there may be a gold standard diagnostic approach, this flexibility is desirable in programme monitoring and epidemiology as it allows for as much data collection as possible from all countries, no matter which diagnostic technologies are available.

Additionally, this reporting framework includes outcomes not suited to answering questions about clinical effectiveness. For example, the World Health Organisation's set of treatment outcomes includes composite outcomes – specifically, 'treatment success', defined by the World Health Organisation as "a patient who was cured or who completed treatment" (World Health Organisation, 2013b). Effectiveness researchers may be interested the constituent parts of this outcome – that is, cure and treatment completion – but the combination of these into an overarching outcome can be misleading, especially because the size of each component's treatment effect would likely vary, and each component may have a different clinical importance. The combination of cure and treatment completion into one outcome means losing the specificity (and the 'directness') of the constituent data for answering a clinical question. Furthermore, 'treatment completion', defined as treatment completed as prescribed without evidence of failure but also without evidence of cure, is not a clinically useful measure of adherence. It is the number considered to be adherent (the clinically useful statistic) without those who are also considered to be cured, which provides an incomplete picture of treatment compliance.

In addition to being unsuited to use in effectiveness trials in their current form, the World Health Organisation's set of treatment outcomes do not address the two other key objectives of COS: to ensure that trial data is useful to patients and clinicians, and to minimise outcome selection/reporting bias. On examination of the composition of the groups involved in developing the World Health Organisation's reporting framework, it is apparent that there has been little patient or even clinician involvement (World Health Organisation, 2013b). The groups that have developed the various iterations of the reporting framework over the years have predominantly been made up of a combination of policy-makers and programme directors, as well as a small number of academics and researchers. Furthermore, given that the outcomes are not promoted as a core set that should be measured, as a minimum, in all TB trials, it is unlikely that the World Health Organisation's set of treatment outcomes will help in minimising outcome selection/reporting bias.

Beyond the World Health Organisation's reporting framework, little other work that has been conducted into outcome definition and prioritisation for TB. This research project will trial some of the emerging methods for COS development taking tuberculosis as a case study. In addition to exploring COS methods, this work will therefore seek to provide a valuable tool for use in the development of a COS for TB, and beyond that for future clinical trials.

An overview of methods for developing core outcome sets

This chapter will explore the methodology currently used in the development of COS. Particular attention will be given to the research designs used and to who should be involved in this process, exploring the needs and challenges associated with patient and public involvement in COS development.

COS methodology has been the focus of much study in recent years, undergoing and continuing to undergo considerable evolution. The exact approach taken may vary from COS to COS, depending on the resources available, the stage of development, the iteration of the COS, the condition and population of interest, and so on, but there is little argument that the development of COS can and should include a range of both quantitative and qualitative methods, as well as a range of contributors, selected due to their skills, experience, view points and interest in the outputs of clinical research.

SYSTEMATIC REVIEWS OF OUTCOMES USED IN CLINICAL TRIALS

Systematic reviews have been central to the definition of outcome sets since the development and publication of the first COS, by OMERACT, in 1993 (Felson *et al.*, 1993).

> *"A systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question. It uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing more reliable findings from which conclusions can be drawn and decisions made." (Higgins and Green, 2011)*

In COS development, past clinical trials are systematically reviewed and the range of outcomes that have been used and the rationales provided for these, where given, are documented. This process allows COS developers to get a sense of current and past thinking on outcome selection (Williamson, *et al*., 2012a), it can be useful in identifying the scale of any current problems (such as the diversity of outcomes used, as well as any inconsistencies or outcome selection/reporting bias) and it can provide a preliminary list of outcomes for consideration.

Currently, the COMET database lists 140 published papers relating to the development of COS that have included systematic reviews, with a further 101 that have yet to be published (available at: http://www.comet-initiative.org/studies/search; accessed: 10 December 2015).

Although the earliest methodology used in COS development (Felson *et al.*, 1993), the review of previously used outcomes alone does not allow a set of outcomes to progress. As discussed in the previous chapter, the outcomes reported in trials are not always the most appropriate to clinical decision-making and maintenance of the *status quo* does not enable the full potential of COS to be realised. For this reason, more 'generative' methods, which explore not which outcomes *are* used but which outcomes *should be* used, have been added to COS methodology.

INTERVIEWS, FOCUS GROUPS, SURVEYS

Seeking to move beyond existing practice has led COS developers to elicit views on the relative importance of different outcomes from stakeholders. There are various social research designs through which COS developers can elicit the views of stakeholders, but most common are the following: interviews, focus groups and/or surveys.

Interviews tend to occur one-on-one, whereas focus groups and surveys seek information from groups of people at the same time. Interviews and focus groups tend to be face-to-face, although telephone and video technologies now mean they can also be conducted from a distance, whereas a survey uses a questionnaire to allow data to be collected from a distance. Interviews and focus groups tend to be more unstructured or semi-structured, allowing participants to expand their answers, providing more detailed accounts of their experiences and feelings. Surveys are generally structured, although some researchers may choose open questions if they wish to be more exploratory.

Interviews and focus groups tend to be considered qualitative methods; they are often well-suited to areas of research in which there is considerable uncertainty, areas of research in the early stages of development, or areas of research that are primarily concerned with exploring people's subjective, lived experiences or personal beliefs. Focus groups "have the advantage of making use of group dynamics to stimulate discussion, gain insights and generate ideas in order to pursue a topic in greater depth", with the potential "benefit over individual interviews in that participants will stimulate topics of discussion amongst themselves, which may create a richer source of data." (McAllister, *et al*., 2007). One-to-one interviews, on the other hand, allow for more intimate interactions in which confidentiality can be more easily protected, which can be preferable if the research area is sensitive in some way. Surveys are generally considered to be quantitative, and are more suited to areas in which views on a limited scope of question are sought from a large number of participants who may be spread over a wide geographical area.

In COS development, these techniques are used to elicit views from stakeholders about their experiences of the clinical condition of interest and about relative importance of different outcomes, with the intention of producing a discrete set of clearly defined outcomes considered most critical to patients and to clinical decision-making.

An examination of the COMET database shows that all three of these approaches have been used in the development of COS. Currently, the database lists 178 published papers relating to the development of COS that have included interviews or focus groups (including 'semi-structured discussion') and 35 using surveys, with a further 74 and 15, respectively, that have yet to be published (available at: http://www.comet-initiative.org/studies/search; accessed: 10 December 2015).

GROUP DECISION-MAKING AND CONSENSUS METHODS

Group decision-making possesses a number of benefits over individual decision-making: "a wider range of direct knowledge and experience is brought to bear; the interaction between members stimulates consideration of a wide range of options and debate that challenges received ideas and stimulates new ones; idiosyncrasies are filtered out … ; and, in terms of influencing the behaviour of others, the group as a whole may carry more weight than any one individual." (Murphy, et al., 1998). However, achieving agreement as a group is not always straightforward, so consensus methods are used to achieve agreement – or assess the extent of agreement – within a group.

In the context of COS development, consensus methods are used to achieve agreement – whether by discussion or survey – as to the outcomes that should be included in the set.

> *"The procedures have three features: (1) Anonymous response – opinions of members of the group are obtained by formal questionnaire. (2) Iteration and controlled feedback – interaction is effected by a systematic exercise conducted in several iterations, with carefully controlled feedback between rounds. (3) Statistical group response – the group opinion is defined as an appropriate aggregate of individual opinions on the first round. These features are designed to minimise the biasing effects of dominant individuals, of irrelevant communications, and of group pressure toward conformity." (Dalkey, 1969)*

The anonymity of consensus methods mitigates against some of the pitfalls often associated with decision-making in groups. For example,

> *"Groups or committees … are commonly dominated by one individual or by coalitions representing vested interests. In open committees individuals are often not ready to retract long held and publicly stated opinions, even when these have been proved to be false." (Jones and Hunter, 1995)*

Anonymity in the process reduces the opportunity for such grandstanding. It reduces the opportunity for "direct confrontation … [which] all too often induces the hasty formulation of preconceived notions, an inclination to close one's mind to novel ideas, a tendency to defend a stand once taken or, alternatively and sometimes alternately, a predisposition to be swayed by persuasively stated opinions of others" *(Dalkey and Helmer, 1963)*

The iterative nature of the process allows participants to be considered and hear rationales for a range of ideas, formulate opinions and then reconsider these based on those of the rest of the group. It allows ideas – both at the level of the group and at the level of the individual – to develop and be refined. Over a number of iterations, it is expected that views will converge towards a consensus.

The third feature of consensus methods – the statistical characterisation of the group's opinion – means that this technique is generally, like the survey or questionnaire, considered a quantitative social research methodology. The feedback allows participants to reconsider and revise their views in light of those of the rest of the group.

The most commonly used consensus methods in COS development are the Delphi technique and the nominal group technique, though others also exist.

The Delphi technique "comprises sequential questionnaires answered anonymously by a panel of participants with relevant expertise. After each questionnaire, the group response is fed back to participants." (Sinha, *et al.*, 2011). Traditionally the Delphi technique is enacted through a questionnaire (see, for example, McGrath, *et al.*, 2008; Payne, *et al.*, 2007; Schmidtt, *et al.*, 2010; Serrano-Aguilar, *et al.*, 2009; Sinha, *et al.*, 2012; Smaïl-Faugeron, et al., 2013), but other approaches such as face-to-face group meetings can be used. The questionnaire approach has the advantages of complete anonymity and the facility to involve a large number of participants from a wide geographical area. However, face-to-face group meetings allow for some interaction and discussion between participants, whilst maintaining anonymous voting.

> *"Despite its usefulness, Delphi has some notable limitations. For example, its reliability increases with the size of the group and the number of rounds, but panellists sometimes become fatigued after two or three rounds, and coordinating large groups and several rounds can be complicated and costly." (Fink,* et al.*, 1984)*

The second key consensus method used in COS development is the nominal group technique (see, for example, Douglas, *et al*., 2009; Howell *et al*., 2012; Lamb, *et al*., 2005; Ruperto, *et al*., 2006).

> *"Firstly, each participant records his or her ideas independently and privately. The ideas are the listed in a round-robin format, that is one idea is collected from each individual in turn and listed in front of the group by the facilitator, and the process is continued until all ideas have been listed. Each idea is then discussed in turn by the group. Individuals then privately record their judgements or vote for options. Further discussion and voting may take place. The individual judgements are aggregated statistically to derive the group judgement." (Murphy,* et al*., 1998)*

Despite the usefulness of these techniques, reviews of the current COS literature have shown that many groups do not use structured consensus methods, instead relying on semi-structured discussion. For example, the greater prevalence of semi-structured discussion was noted in the systematic review of studies that develop or apply methodology for selecting outcomes to be used in clinical trials in children (Sinha, *et al*., 2008). It is unclear why this approach remains widespread, given the drawbacks that can occur when there are imbalances in group dynamics, although the higher cost and planning requirements may play a role.

Currently, the COMET database lists 124 published papers relating to the development of COS that have included consensus techniques, with a further 113 that have yet to be published (available at: http://www.comet-initiative.org/studies/search; accessed: 10 December 2015).

WHO TO INVOLVE

As stated above, primary research in which investigators elicit views from various stakeholders, in a process of collaborative COS development, is central to COS methodology. Historically, this research (in the form of interviews, focus groups or surveys) focused almost exclusively on 'expert' opinion – that is, the views of clinicians and, more frequently, researchers. For example, one systematic review of studies engaged in COS development found that,

> *"Initiatives to identify which outcomes to measure in clinical trials … focus on the opinions of researchers. This means that outcomes included in existing core sets may be selected to serve the needs of researchers in academia or industry, rather than considering how important they are to patients." (Sinha,* et al*., 2011)*

However, it is increasingly recognised that the development of COS requires the input of a much more diverse spectrum of stakeholders, including patients, carers, members of the public

more generally, regulators and industry representatives in addition to clinicians and researchers (Williamson, *et al*., 2012a).

One systematic review of 25 studies, conducted by 13 groups, that develop or apply methodology for selecting outcomes to be used in clinical trials in children (Sinha *et al*., 2008) empirically demonstrated the breadth of expertise and experience sought out by COS developers. All 13 groups included clinicians and researchers with a range of specialties or interests. Three groups included parents or carers of children, but no group involved children directly. Given the difficulties of including children in research, the complexities of some of the concepts under consideration and the stringent requirements for ethics approval of research involving children, this is perhaps unsurprising, though gaining some indication of the views of children would still be desirable. Three groups included representatives from industry and/or drug regulatory authorities such as the Food and Drug Administration.

Including such a broad array of contributors is not always straightforward, but it is essential in ensuring that the COS is relevant and useful to all those that it is hoped will use the outputs of future clinical research. Central to this is ensuring that COS – and the research they are to help shape – are patient-centred, meaning that COS development must have a certain degree of patient involvement. This is a principle very much in line with the prevailing concept of patient involvement in healthcare more generally.

> *"Public involvement in research is founded on the core principle that people who are affected by research have a right to have a say in what and how research is undertaken." (Staley, 2009)*

Patient and public involvement will help to target resources towards issues of importance to patients, which is itself important in ensuring that the data we collect is clinically useful to patients, and can help in empowering them in making decisions about their own care.

UK research policy explicitly stresses the need to "involv[e] more people, patients and healthcare professions in high-quality research" (Department of Health, 2006):

> *"We know from our experience that engaging patients and members of the public leads to research that is more relevant to people's needs and concerns, more reliable and more likely to be put into practice. To achieve this, patients and the public must be involved in all stages of the research process: priority setting; defining research outcomes; selecting research methodology; patient recruitment; interpretation of findings; dissemination of results." (Department of Health, 2006)*

The importance of patient and public involvement in research has further been recognised, for example, in recent regulatory guidance from the United States: documented evidence of patient input in the development of instruments for the measurement of patient-reported outcomes is now a requirement for obtaining approval for labelling on medical products that these outcomes

are designed to inform (United States Food and Drug Administration, 2009). Without obtaining this approval, companies will not be able to sell the medical product in question in the United States.

Additionally, the influence of public involvement in research was evaluated in the INVOLVE study, conducted on behalf of the United Kingdom's National Institute for Health Research, in which a structured review of the literature sought to demonstrate the benefits brought to research by such involvement, as well as highlight where and when it has the greatest value (Staley, 2009). The review found that public involvement has shaped the research agenda in a number of ways, through the identification of research topics, helping to shape the research questions investigated, and contributing to decisions about which projects should receive funding. Further to this, the INVOLVE study found public involvement to have had a positive influence at all stages of the research cycle, including study design, participant recruitment, data collection, data analysis, reporting and dissemination. Similar positive findings have been found by other reviews of patient and public involvement in clinical research (see, for example, Brett, *et al*., 2012; Carter, *et al*., 2013; Garces, *et al*., 2012; Nilsen, *et al*., 2006)

Patient and public involvement in COS development, and in the shaping of clinical research more generally, should additionally help to bridge the gap between technical, or 'expert', knowledge and experiential knowledge: although the views of patients and 'experts' are both valuable in shaping clinical research, they are not always the same. For example, early versions of the OMERACT COS for rheumatoid arthritis had no patient involvement in their development, focusing instead on clinicians and researchers (see, for example, Tugwell and Boers, 1993a; Tugwell and Boers, 1993b; Bellamy, *et al*., 1995; Bellamy, *et al*., 1997; Wolfe, *et al*., 1999). It wasn't until patients became involved in 2002 that fatigue was recognised as an important consideration in rheumatoid arthritis (Kirwan, *et al*., 2003). Fatigue as a core outcome was validated through an OMERACT research agenda and, in response, more effective tools for measuring fatigue in rheumatoid arthritis have been devised and increasingly used in clinical trials (see, for example, Hewlett, *et al*., 2007; Nicklin, *et al*., 2010). Similarly, patients highlighted a number of previously unidentified outcomes and outcome domains following their involvement in the revision of the IMMPACT COS for chronic pain (Turk, *et al*., 2008). Numerous other examples of differences between patient and clinician or researcher views on the importance of outcomes exist, including in the selection of outcomes for trials in clinical genetics and genetic counselling (Payne, *et al*., 2007), fibromyalgia (Mease, *et al*., 2008), degenerative ataxias (Serrano-Aguilar, *et al*., 2009) and diabetes (Gandhi, *et al*., 2008). These differences mean that clinicians and researchers alone cannot formulate valid, useful COS – patient involvement is key.

In stressing the importance of patient and public involvement in research, however, it is also important to consider the impact it might have on those patients and members of the public who participate. The INVOLVE study also considered these aspects in their structured review:

> *"The evidence suggests that public involvement has both positive and negative impacts on the public involved. The positive benefits include: acquiring new skills and knowledge; personal development; support and friendship; enjoyment and satisfaction; being rewarded financially. There are fewer reports of involvement having a negative impact on the people involved, but in these cases, the public have had a bad experience as a result of being: emotionally burdened; overloaded with work; exposed through the media; frustrated at the limitations involvement." (Staley, 2009)*

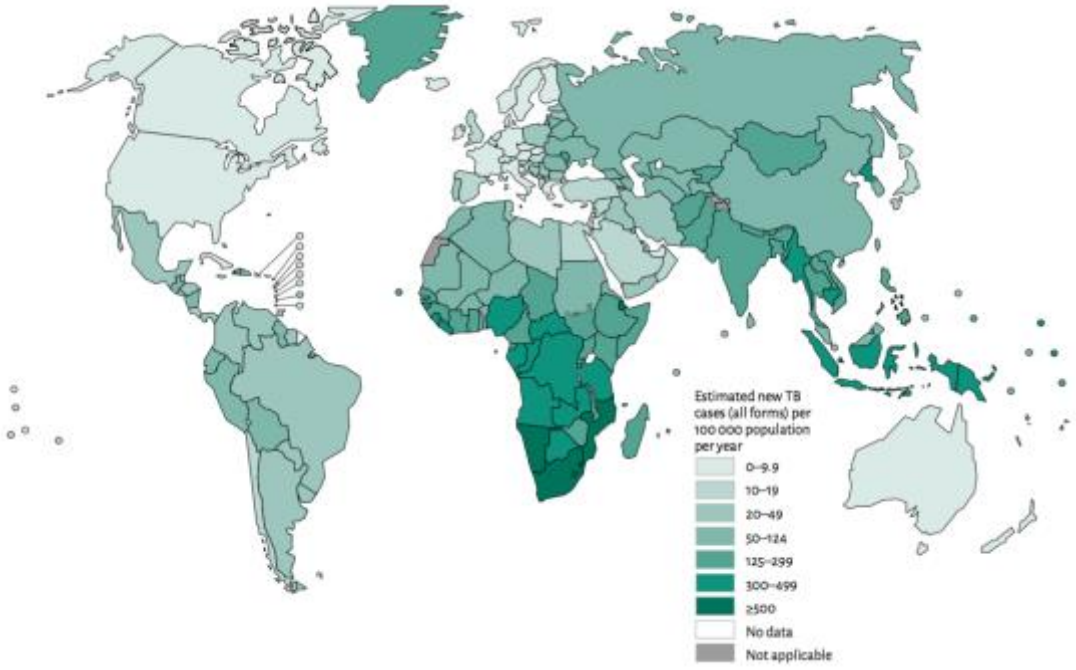
Whilst there are clear benefits to patient and public involvement in research – for both the research and those involved – acknowledging the possible negative effects of research participation is important, and COS developers should tackle these early on. Other challenges include patients' doubts about their ability to contribute and the value of that contribution once made, and concerns over their limited technical understanding or knowledge, as well as researchers adjusting to the involvement of lay people, facilitating them in making valuable contributions and ensuring they avoid tokenism (Morrow, *et al*., 2010). With appropriate preparation, however, these challenges can be overcome. For example, one Delphi study, conducted by Boote *et al*. (2006), highlighted the following as key principles for successful involvement of patients and the public in NHS research: roles of participants should be agreed between the researchers and participants; researchers should budget appropriately for the costs of patient and public involvement; researchers should respect the diverse skills, knowledge and experience of patients and the public; participants should be offered training and support to facilitate their involvement; researchers should take the necessary steps to ensure that they have the skills required to involve patients and the public in the research process; participants should be involved in writing research reports; and the findings of the research should be presented to patients and the public in language and formats that are readily accessible.

Currently, the COMET database lists 114 published papers relating to the development of COS that have included 'consumers', service users and/or patient or support group representatives, with a further 114 that have yet to be published (available at: http://www.comet-initiative.org/studies/search; accessed: 10 December 2015).

A second element of 'who to involve' relates to seeking a range of international perspectives. Clinical conditions may occur at a higher incidence in some countries or regions than in others, but there are few that are relevant to just one country. Tuberculosis, for example, is spread across the world (see Figure 2) with hotspots of high incidence found even in countries considered to have a low burden of the disease. If COS are to be used globally for all research on a particular disease, perspectives from all around the world will be needed, in settings and populations with a range of health, social and economic profiles. In the case of a

COS for tuberculosis, particular efforts should be made to gather the views of people in the hard-to-reach groups that are particularly affected by the disease, such as those with a history of homelessness, imprisonment or substance misuse. TB treatment and prevention services and other public, voluntary or nongovernmental organisations working with people from hard-to-reach groups would be useful partners in identifying and engaging such individuals in focus groups and interviews, or in the consensus exercises that occur in the ratification phase of COS development.

Figure 2. Estimated TB incidence rates, 2014 (reproduced from World Health Organisation, 2015)



In recognition of the importance of the inclusion of a numerous and diverse array of patients in COS development, this research project will examine patient perceptions of TB treatment outcomes and their relative importance through a trial of systematic reviews of qualitative social research, a previously unexplored realm of methodology for COS development.

Exploring the use of qualitative systematic reviews in the development of core outcome sets:

the methods

This chapter will explore the methodological decisions to be implemented within the proposed research, examining systematic reviews of qualitative research, their methodology, their potential within COS development and the means by which this research project shall examine such potential.

A NEW ADDITION TO CORE OUTCOME SET METHODOLOGY: QUALITATIVE SYSTEMATIC REVIEWS

> *"Qualitative research is concerned primarily with how people see and understand their social worlds … Assembling the findings of multiple primary qualitative studies using a systematic process may have a number of additional benefits: they may help generate more comprehensive and generalisable theory; [or] they may add greater breadth and depth to existing systematic reviews." (Atkins* et al., 2008*)*

In addition to quantitative reviews of outcomes in the current evidence base, this research project proposes that systematic reviews of qualitative research might have potential within COS development to increase the volume, depth and diversity of stakeholder – specifically patient – perspectives.

QUALITATIVE RESEARCH

> *"In qualitative research, the results are not products of statistical processes or other quantitative methods. Qualitative research offers insights into social, emotional and experimental phenomena." (SBU, 2014)*

Qualitative research is generally undertaken with the intention of gaining a deeper, richer understanding of experiences, beliefs, behaviours and culture. These phenomena are interpreted in terms of the meanings people attach to them, and are studied in their 'natural'

setting using an array of methods. Some of the approaches relevant to this research project are detailed below.

Grounded theory is an inductive methodology in which theory emerges directly from a body of data in a continually comparative method: "the data itself defines the boundaries and directs development of theory." (Joanna Briggs Institute, 2011). A wide variety of study designs are used to collect data, including focus groups, interviews and field work. In a process of open coding, and without waiting until data collection has been completed (that is, data collection and analysis occur contemporaneously, with one feeding into the other), the researcher appraises the transcripts and field notes and assigns each phenomenon or event a code reflecting its content. Common codes are then aggregated into categories.

A similar – and often confused with – methodology is qualitative content analysis. As with grounded theory, content analysis involves the researcher appraising and coding transcripts and field notes; however, where grounded theory is purely inductive, content analysis can be either inductive or deductive:

> *"An inductive approach is appropriate when prior knowledge regarding the phenomenon under investigation is limited or fragmented. In the inductive approach, codes, categories, or themes are directly drawn from the data, whereas the deductive approach starts with preconceived codes or categories derived from prior relevant theory, research, or literature. The deductive approach is appropriate when the objective of the study is to test existing theory or retest existing data in a new context." (Cho and Lee, 2014)*

Ethnography, another widely employed approach to qualitative research, seeks to understand experiences, beliefs and behaviours within a culture from the perspective of those within that culture. Although the word 'ethnography' is not used consistently in the literature, it always involves a significant amount of "direct and sustained social contact with agents, and of richly writing up the encounter, respecting, recording, representing at least partly *in its own terms*, the irreducibility of human experience"; it is the "witness-cum-recording of human events" (Willis and Trondman, 2000).

A range of others exist. Phenomenology seeks to comprehend "people's individual subjective experiences and interpretations of the world" (Joanna Briggs Institute, 2011), whereas phenomenography "is intended to highlight individuals' various impressions of a phenomenon" (SBU, 2014). Hermeneutics is concerned with the analysis and interpretation of texts, whereas discourse analysis is concerned with the interpretation and understanding the historical and social construction of language. All of these methods are underpinned by a variety of methodological and philosophical frameworks or assumptions, and are enacted through a variety of research designs. It is not the intention of this report to provide a comprehensive list of all, rather to highlight the most relevant to the proposed review. It is notable, however, that the identification of qualitative approach is notoriously poorly defined in study reports (for example,

see Atkins *et al*. (2008) and Campbell *et al.* (2003)), which can further blur the already hazy line between between some of these methodologies.

SYSTEMATIC REVIEWS OF QUALITATIVE EVIDENCE

> "*Literature reviews accumulate learning and avoid the pitfalls of relying on single studies. Systematic reviews apply explicit methods to this task, such as comprehensive searching and the quality assessment of studies. There are therefore good reasons for applying systematic review methods to views studies." (Harden* et al*., 2004)*

Currently, qualitative evidence synthesis is not an accepted component of COS methodology (though this is unsurprising given the relative nascency of qualitative synthesis methods). However, this research project proposes that a review of, for example, patient views on the relative importance of different treatment outcomes, or more indirectly of living with a disease or making decisions about its management, and integration of this into the development of a COS will improve the volume, depth and diversity of the views incorporated into the COS.

> *"In the past, qualitative researchers have failed to cite other similar research on relevant topics leaving findings isolated, and resulting in information, concepts and theories about a topic that are not built upon or developed … Pragmatically, the failure to synthesise may also be seen as wasteful, since it does not optimise the use of previous findings and the contributions of individual researchers to a body of knowledge." (Garside, 2008)*

The potential of systematic reviews of qualitative research on perspectives has already been highlighted in other areas. For example, one review of perspectives and experiences relating to young people's mental health, physical activity and diet concluded that,

> *"reducing the potential for bias is a key strength of systematic reviews. We identified two other strengths of a systematic approach to reviewing research: greater breadth and greater depth." (Harden* et al*., 2004)*

The reviewers found that the synthesis of multiple studies allowed a sizeable volume of young people (37,335, based on the 33 studies that reported a sample number) from diverse groups to contribute their views. There was, for example, comprehensive consideration and coverage of gender across the studies, although the review also highlighted the inadequate reporting of socioeconomic characteristics and information relating to ethnic background: "the analysis

offered a clear message to researchers to describe the social characteristics of their samples more carefully" (Harden *et al*., 2004).

Though qualitative synthesis may provide useful perspectives to the development of COS, the methods are less well-developed than for other areas of COS methodology and a number of issues persist in causing problems. For example, at one level the divergent assumptions – particularly theoretical and philosophical assumptions – that underline different approaches to qualitative research might limit the validity of pooling studies using different methodologies.

> *"It is difficult to discern the impacts that the theoretical orientation of the researchers had on the analysis process itself, and how the findings might have been presented differently if another theoretical framework had been adopted. This raises the question of whether papers from different theoretical perspectives should be synthesized, as it is likely that these different approaches impact on both the framing of the research question and the interpretation of data." (Atkins* et al*., 2008)*

At another level there is the question of whether or not it is valid to synthesise studies from differing sociocultural contexts (in terms of the setting or the populations studied) or in which the primary phenomena of interest are not the same:

> *"To summarise qualitative findings is to destroy the integrity of the individual projects on which such summaries are based, to thin out the desired thickness of particulars... and ultimately to lose the vitality, viscerality and vicarism of the human experiences represented in the original studies." (Sandelowski, 1997)*

Pooling these requires the reviewer to carefully consider the transferability of the results across contexts (SBU, 2014). In the context of COS development, however, it is exactly this breadth of contexts which is appealing – a COS should be internationally relevant, taking into account the views and perspectives of all those whom clinical effectiveness research might affect, across a spectrum of sociocultural contexts.

A SYSTEMATIC REVIEW OF PATIENT PERSPECTIVES ON TUBERCULOSIS TREATMENT OUTCOMES

This section gives an overview of and explanation for the methods employed within this research project.

SCOPING

Having decided to undertake a systematic review of qualitative research concerning patient perspectives on TB treatment outcomes, scoping searches were performed. These should be carried out at the start of any systematic review – qualitative or quantitative – for a number of reasons (Booth, 2011; Joanna Briggs Institute, 2011; SBU, 2014). Firstly, to identify any existing reviews and confirm the need for a review, as well as provide 'seed reviews' and key studies which could offer a starting point for the proposed review. Secondly, to further inform the development of the review question and review protocol. And finally, to assist in the development of the search strategy by familiarising the reviewer with key terms.

First, Google Scholar was informally searched for relevant papers. Then, the Cochrane Qualitative Evidence Synthesis Register and MEDLINE were searched for other qualitative systematic reviews (see Table 1 for the strategies used). The Cochrane Qualitative Evidence Synthesis Register was searched for Cochrane and 'other reviews' using TB terms. No methodological terms or filters were used because this database, as the name indicates, is a repository specific to qualitative evidence reviews. For the MEDLINE search, TB terms (including a MeSH heading) were combined with qualitative synthesis filter (Booth, 2011). From a practical perspective, an English language restriction was applied to both scoping searches, as were a human-only restriction (the review is not concerned with non-humans) and a full text-only restriction (abstracts do not possess sufficient levels detail to understand methods or appraise quality).

Table 1. Scoping search strategies

Database	*Terms*	*Other limits*	*Date*	*Retrievals*
Cochrane Qualitative Evidence Synthesis Register	Tuberculosis OR 'TB'	Cochrane reviews and 'other reviews' English language	Up to 10th August 2014	10
MEDLINE	(exp tuberculosis/ OR "TB" OR tuberculo*) AND (qualitative systematic review* OR (systematic review AND qualitative) OR evidence synthesis OR realist synthesis OR (qualitative AND synthesis) OR meta-synthesis* OR meta synthesis* OR meta synthesis OR meta-ethnograph* OR metaethnograph* OR meta ethnograph* OR meta-study OR metastudy OR meta study)	English language Full text Human	Up to 10th August 2014	715

The Cochrane Qualitative Evidence Synthesis Register yielded 10 papers, and MEDLINE 1,203; however, no papers were ultimately found to be directly relevant. A number of qualitative systematic reviews examining phenomena other than treatment outcome prioritisation (including TB-related stigma and treatment adherence) but which examined other beliefs or experiences relating to TB were identified; for example, see Atkins *et al*., 2008; Juniarti and Evans, 2011; Krishnan *et al*., 2014; Munro *et* al., 2007; Noyes and Popay, 2007. Although not strictly relevant to the review question, the references of these were checked. Information gathered from the reviews and from the included papers were used to increase background knowledge of the research area, refine the review question and develop the review protocol and search strategies. For example, the TB terms expanded from Tuberculosis and 'TB' to also include tuberculous, antitubercular and mycobacteria.

THE REVIEW PROTOCOL

The review protocol (see Table 2) was formulated using the 'SPICE' framework, in which S denotes the setting or context of interest, P the perspective or population, I the intervention or the phenomenon of interest, C the comparison and E the evaluation (Booth, 2004).

In keeping with the aspiration that this review will enable a broad range of views to be considered, the setting and location were kept inclusive. For the same reason, no age limit was applied to the population: the views of children and of adults with the disease are equally desirable. However, a diagnosis – or previous diagnosis – of TB is a prerequisite to inclusion. Furthermore, patients with significant comorbidities or coexisting conditions that might affect the management or experience of their TB are excluded. The major subgroup affected by this exclusion is anticipated to be those with HIV. In 2014, an estimated 12% of people who developed TB worldwide and an estimated 25% of all TB deaths were in people with HIV (World Health Organization, 2015). Co-management and co-experience of TB in this population can significantly differ from the management and experience of the disease in those with TB alone, and should therefore be considered by a separate review. However, in recognition of the fact that HIV status is not always explicitly reported in studies, where this population characteristic is not reported it will be noted in the assessment of the study quality along with the prevalence of HIV in the country in which the study was conducted. Furthermore, a human-only restriction was once again applied.

In terms of study design, any study using qualitative methods of analysis to describe patterns or themes raised by participants through direct contact with patients or direct observation was considered for inclusion. An English language restriction was once again applied for the sake of practicality, as was a full text-only restriction, and a date range of 2003 to the present (inclusive) was also applied. Although selection of the precise date for cut-off could be fairly arbitrary, very old studies may be unsuitable as they present historical rather than

current experience and views; a cut-off of 2003 was chosen a) to limit the inclusion of outdated views and b) to coincide with the introduction of the MeSH heading for qualitative research (another practical consideration).

Table 2. Review protocol

Setting	Any setting or geographical location
Perspective	Any age Diagnosed, or previously diagnosed, with tuberculosis No significant comorbidities that might affect the management of their TB Excluded populations: - no diagnosis of tuberculosis - mixed groups of participants e.g. patients and carers or health care providers, unless results from patients are explicitly separate from other participants - significant comorbidities that might affect the management of their TB e.g. HIV
Intervention	Patient experience or views on the outcomes of TB treatment
Comparison	None

Evaluation	Studies using qualitative methods of analysis to describe patterns or themes raised by participants through direct contact with patients or direct observation; this includes: - qualitative studies - studies involving secondary qualitative analysis of qualitative data - a qualitative study as part of a mixed methods study - Excluded designs: ● lexical studies that analyse natural language data presented as quantitative results ● social research methods using questionnaires or other methods that do not involve direct contact or observation of participants ● any study where qualitative data not analysed i.e. uninterpreted data ● any review (systematic, narrative, qualitative) – relevant primary studies will be considered for direct inclusion ● any quantitative study, (RCT, non-RCT, observational, cohort, case control) ● treatment guideline documents ● commentary articles, written to convey opinion or stimulate research or discussion, with no research component English language Publication date: 2003-present (inclusive) Fully published reports e.g. not conference proceedings or abstracts Peer-reviewed e.g. dissertations /theses

THE LITERATURE SEARCH

The difficulties of searching for and retrieving relevant qualitative research have been widely reported (for example, Barroso *et al*., 2003; Campbell et al (2003); Evans, 2002). These challenges include the tendency towards ambiguous, uninformative titles, the use of unstructured and enigmatic abstracts which lack important information, and the use of little or no indexing in databases (Booth, 2011; Johnson, 2013). Where indexing has been attempted, there are "discrepancies in the database indexing and/or the abstracts of the articles" (SBU, 2014). Challenges such as these have led the search for relevant qualitative evidence to be likened to "berry-picking":

> *"Searching for qualitative research reports … is similar to collecting wild berries. The process cannot be definitively mapped from the outset, nor is it easily reconstructed at the conclusion. The route involves many twists and turns and to-and-fro movements that defy simple cartography." (Johnson, 2013)*

The impact of these challenges on the approach to searching is demonstrated in Greenhalgh *et al*.'s (2005) systematic review of the data sources used in complex evidence: just 30% of 495 studies to have been identified using a protocol (that is, the search strategy was defined at the start of the study). Many studies had made use of a range of other search methods, most notably "snowballing" (51%), in which the search strategy "emerg[ed] as the study unfolded". Personal knowledge (24%) and reference tracking (44%) also made significant contributions to the evidence base.

For the present review, the published literature was systematically searched in a number of general and subject-specific databases: ASSIA, CINAHL, Embase, MEDLINE, and PsycINFO (see Table 3 for full details of the strategies used). The lack of directly relevant studies identified in scoping meant that the design of a search strategy that is both sensitive (that is, a large proportion of relevant papers identified against the total number of relevant papers in existence) and precise (or a large proportion of relevant papers identified against the total number of reports identified) was a considerable challenge. However, the anticipated paucity of directly relevant studies ultimately meant that a broad strategy was adopted, even with the acknowledgement that this might have a significant impact on the time required to sift through the retrieved studies.

As stated above, qualitative research suffers from poor indexing, so the strategy employed a combination of index and free-text terms relating to qualitative research and tuberculosis (again, see Table 3). It was felt that this would enable a sufficiently broad strategy to capture as many qualitative studies examining patient perspectives and experiences of TB

and its treatment as possible. In line with the principle highlighted in Greenhalgh *et al*. (2005) – that searches for qualitative research should not rely exclusively on predefined, protocol-driven search strategies – the initial inclusion of patient terms was abandoned. This was because, when tested without these terms, it was found that the strategy missed potential inclusions.

For the reasons stated above (see 'The review protocol'), an English language restriction and lower date threshold down to (and including) 2003 were applied to all searches.

Table 3. Search strategies

Database	*Terms*	*Other limits*	*Dates*	*Retrievals*
ASSIA	(SU.EXACT("Tuberculosis") OR TB OR tubercul*)	English language	1st January 2003 to 5th December 2014	717
CINAHL	((MH "Qualitative Studies+") or (MH "Focus Groups") OR (MH "Content Analysis") OR (MH "Grounded Theory") or (MH "Ethnographic Research") OR ((qualitative* N2 (research OR stud* OR analysis OR method* OR approach* OR data)) OR focus group* OR meta synthesis OR interview* OR grounded theor* OR ((content or conversation) N1 analysis) OR ethnograph* OR group discussion*)) AND ((MH "Tuberculosis") OR "TB" OR tuberculo* OR antituberculo* OR mycobacteri*)	English language Full text	1st January 2003 to 5th December 2014	447
Embase	(exp qualitative research/ or exp content analysis/ or exp interview/ or exp grounded theory/ or exp ethnography/ or ((qualitative adj2 (research or stud$3 or analysis or method? or approach$2 or data)) or focus group? or meta synthesis or interview? or grounded theor$3 or ((content or conversation) adj1 analysis) or ethnograph$ or group discussion?).mp.) and (exp Tuberculosis/ or TB.mp. or tuberculo$.mp. or antitubercular.mp. or mycobacteri$.mp.)	English language Full text Human	1st January 2003 to 5th December 2014	510

MEDLINE	(((exp qualitative research/ OR exp interviews as topic/ OR (qualitative adj (research OR study OR analysis OR method? OR approach$2 OR data)) OR focus group? OR meta synthesis OR interview? OR grounded theory OR ((content OR conversation) adj analysis) OR ethnography OR group discussion?)) AND ("semi-structured" OR semistructured OR unstructured OR informal OR "in-depth" OR indepth OR "face-to-face" OR structure OR guide interview* OR discussion* OR questionnaire* OR focus group* OR qualitative OR ethnograph* OR fieldwork OR "field work" OR "key informant" OR narration OR conversation)) AND (exp tuberculosis/ OR "TB" OR tuberculous $.mp. OR antitubercular $.mp. OR mycobacteria $.mp.)	English language Full text Human	1st January 2003 to 5th December 2014	387
PsycINFO	((("semi-structured" or semistructured or unstructured or informal or "in-depth" or indepth or "face-to-face" or structured or guide or guides) adj3 (interview* or discussion* or questionnaire*)).ti,ab,id. or (focus group* or qualitative or ethnograph* or fieldwork or "field work" or "key informant")).ti,ab,id. or exp qualitative research/ or exp interviews/ or exp group discussion/ or qualitative study.md. not "Literature Review".md. AND (TB or tuberculo* or antituberculo* or mycobacteri*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]	English language Human	1st January 2003 to 5th December 2014	195

Finally, the references of all identified papers were reviewed for additional inclusions. Given that no directly relevant studies were identified in scoping no authors could be contacted for additional references.

SELECTION OF LITERATURE

The retrievals from each database were scrutinised for inclusion against the criteria set out in the review protocol: first at the level of title and abstract, then at the level of the full paper. Ideally this sifting process should be undertaken by two reviewers as it allows uncertainties to be discussed, and certainties to be confirmed or challenged. However, because the research was the work of one reviewer this could not be done.

EXTRACTION

To aid data extraction from the identified studies, a template was developed. This specified the types of information that should be transcribed from the available reports. Key items included: the citation; the databases in which the paper was identified; the primary aims of the study; details of the study context, population, methods for data collection and analysis, and an overview of the findings; data that is relevant to the review question and which will form the basis of the review findings; critical appraisal (this will be discussed in greater detail below – see 'Critical appraisal').

Because the scoping searches demonstrated a lack of directly relevant studies, it was anticipated that an inclusive approach would be more appropriate in the present review. This means that all relevant data, including author interpretations (known as second level constructs) of the primary data (what was actually said or done by participants – first level constructs), were extracted to ensure that information of potential significance to the findings of the review (third level constructs) is not lost. Any author interpretations would ideally be accompanied by primary data to ensure validity (Noyes and Lewin, 2011), though where this was not possible it was reflected in the assessment of the confidence the reviewer had in the review finding(s) derived (see 'Assessment of confidence in review findings'). This decision was, again, taken in anticipation of the lack of available evidence, but also in recognition of the constraints placed upon published study reports (in terms of, for example, article length or style). There is also a logic that suggests that the inclusion of only primary data and not author interpretation on the basis of validity is a false distinction. This is because, unless *all* relevant primary data is included, selection for inclusion is also an 'interpretation' of the evidence; data is selected to convince the reader of the narrative or argument that the author is giving and as such is as much part of the author's interpretation.

"Accessing first order constructs, or participant views or beliefs, is problematic in the context of a meta-ethnography since the data extracts included in the primary papers have already been selected from the full dataset by the study authors." (Atkins et al., 2008)

CRITICAL APPRAISAL

"The purpose of the critical appraisal of a systematic review is to determine its validity, to interpret their results and to evaluate its applicability in clinical practice, in public health and/or in conducting future studies." (Abalos et al*., 2001)*

Critical appraisal is an enshrined component of systematic reviews of *quantitative* evidence, but its use in systematic reviews of qualitative evidence is not yet universally accepted (for example, Walsh and Downe (2006)). Even those who agree that quality assessment is important fail to agree on the best approach (Sandelowksi & Barosso, 2002). A number of tools exist, including the CASP checklist (Critical Appraisal Skills Programme, 2013), the Joanna Brigg's Institute's Qualitative Assessment and Review Instrument (QARI), the RATS guidelines (Clark, 2003) and the Criteria For The Evaluation Of Qualitative Research Papers from the BSA MedSoc group (Blaxter, 1996), to name a few. Many of these contain broadly similar fields of assessment, but it was felt that the CASP checklist presented a clear, rigorous and usable step-by-step approach.

The CASP checklist covers 10 domains, each addressing an area of potential methodological limitation (Critical Appraisal Skills Programme, 2013). The first domain asks is there was a "clear statement of the aims of the research" and if these are thought to be important and relevant. Then it asks the reviewer to consider whether or not a qualitative methodology was suitable for achieving these aims – that is, if the aim of the research is to describe or interpret the actions and experiences of research participants. If so, is the chosen research design justified? As described above (see 'Qualitative research'), a wide range of qualitative designs are available, each with their own strengths, weaknesses and theoretical underpinnings, and not all will be appropriate for achieving all research objectives.

The next domain considers the approach to sample recruitment, both how the participants were selected and the rationale underpinning this strategy. Will the sample chosen enable "an increased understanding of variations in the phenomenon to be studied" (SBU, 2014)? There are a number of ways that samples can be chosen, including theoretical sampling, in which there is no *a priori* pronouncement about the type and number of participants to be included in the study; the sampling is instead based upon the iterative, inductive progress of the analysis. Another method is purposeful sampling, in which participants are selected to

suit the aims and conditions of the study. Alternatively, a chain sampling or 'snowball' approach can be used, in which participants are asked who else should participate, or a maximum variation approach. Convenience sampling is considered to be of low methodological quality because it is not based on any methodological or theoretical decisions with the aim of achieving the reviews objectives, rather it is based on the accessibility and vicinity of the participant to the researcher.

The reviewer is then asked to consider the approach data collection. Was the location for data collection appropriate? Were the methods clear and were they justified?

> *"The method depends on the topic to be studied. Interviews can be appropriate for the study of experiences (opinions, emotions, needs and desires), while observation is more appropriate for behavioural studies (interpersonal relationships, group dynamics, gender role patterns and so forth)." (SBU, 2014)*

For the present review, interviews and focus groups were considered the most appropriate; direct observation of patients could be useful, though was preferable mostly as an addition to interview or focus group data.

Beyond the approach of data collection itself, was the point at which data collection was *stopped* justified? Did the study employ the principle of data saturation?

> *"In qualitative research, there are no rules about what size a sample needs to be; instead this is generally determined by the need for information. A guiding principle in data collection is data saturation, i.e. the amount of collected data required for a specific study varies according to how rapidly the researcher considers that a stage has been reached where further data collection does not yield further knowledge – in other words, that saturation has been achieved." (SBU, 2014)*

Did the researcher consider their relationship with the participant(s) and with the context or phenomenon of interest, including any 'pre-understanding' or 'baggage'?

> *"Pre-understanding includes the researcher's hypotheses, experiences, professional perspective and the theoretical frame of reference which the researcher brings to the start of the project. In general, pre-under- standing is an important aspect of the researcher's motivation for undertaking research into a certain topic, but it can also restrict his ability to approach a project with openness and the potential to learn from the data collected. The researcher should strive to achieve an active, aware attitude to his pre-understanding." (SBU, 2014)*

Was this 'baggage' also considered in relation to the analysis? What was the approach to analysis? Was the relationship between the data and the author's interpretation clear, and was sufficient primary data presented to demonstrate it? How explicit were the findings and the

authors' views on their credibility? Have ethical issues been tackled, including issues such as informed consent, confidentiality and ethics committee approval?

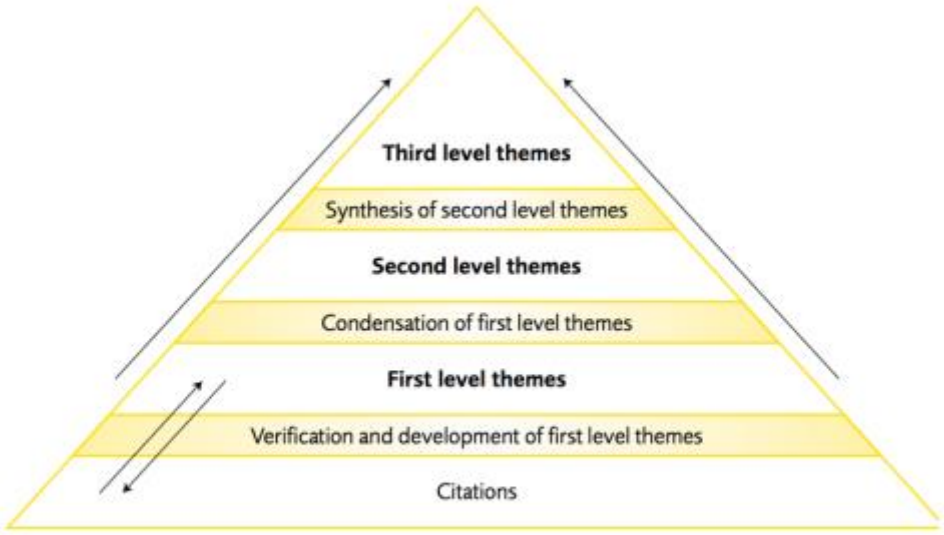
And finally, how valuable is the research? What does it convey about the world, to the world outside of the study context? Can the findings be transferred to other contexts and populations, in particular those of interest in the review?

APPROACH TO SYNTHESIS

> *"A qualitative synthesis uses qualitative methods to synthesize existing qualitative studies to construct greater meaning through an interpretive process .... it involves using a rigorous and methodologically grounded approach for analysis that is filtered through an interpretive lens ... deriving meaning from translation" (Major and Savin-Baden, 2010)*

A range of methods are available for the synthesis of qualitative research which – as with the methods for primary qualitative studies – vary in both the practicalities involved and in the philosophical assumptions that serve as their basis. There also exists a spectrum in their purpose: from the summation and aggregation of constructs (first and second levels) within the primary studies to the construction of 'new' knowledge and theory (third level constructs) (see Figure 3).

Figure 3. Development of third level constructs



The process of synthesis for studies undergoing qualitative analysis

> *"Unlike summative and aggregative approaches to qualitative systematic review where data analysis tends to be linear and the goal is declarative*

statements or directives for action, knowledge-building and theory-generating approaches lend themselves more to iterative data analysis and the goal is concept or theory development." (Johnson, 2013)

Many options across this spectrum are available, including narrative synthesis, meta-synthesis, meta-narrative, meta-summary, meta-aggregation, thematic analysis, grounded theory, meta-ethnography and critical interpretive synthesis (see Table 4 for further details of some of the more widely used methods). Again, as with the methods for primary qualitative studies, the plethora of names depict similar techniques with only slight differences in their actual enactment.

Table 4. Key approaches to qualitative synthesis (adapted from Noyes and Lewin (2011))

Approach	***Description***	***Aggregative or theory-generating?***
Meta-aggregation	The findings from each study are translated into review findings or themes. These themes are illustrated using study quotes and/or by giving an overview of the relevant evidence. Findings are aggregated into categories and then further combined.	Aggregative
Thematic analysis	Important or common themes are identified in the primary studies and thematic analysis used as, or as part of, the synthesis.	Theory-generating and/or aggregative
Grounded theory	In a process of open coding, and without waiting until the identification, review and extraction of studies has been completed, the researcher appraises the primary studies and assigns each phenomenon, event or interpretation of a phenomenon or event a code reflecting its content. The sampling of studies is based on the evolving analysis and stops when theoretical saturation is achieved.	Theory-generating
Meta-ethnography	Reciprocal translational analysis translates findings within the primary studies into context of the other included studies. Those themes that achieve the best overall 'fit' are then further refined into a higher order interpretation.	Theory-generating

The process of choosing a method for the synthesis of the reviews findings began upfront; however, the process was in reality inductive, to some degree driven by the data. The chosen method of synthesis in a qualitative review should be determined by the objectives of review; here the aim was initially thought not to be the generation of an explanatory model or theory, but rather to simply aggregate a diverse range of perspectives and experiences that might inform the development of the COS. For this reason, the initial approach used was that of meta-aggregation, a summative approach that allowed for the concurrent consideration of studies that employed a range of methods and philosophical assumptions. However, this was found to be too simplistic for the needs of the analysis – it generates findings that are not much more than "the sum of its parts" (Sandelowski and Barroso, 2002). The lack of 'direct' evidence (with regards relevance of the evidence to the phenomena of interest) required that this review translate the identified evidence into theories about outcomes, which were not available to simply extract from the data. Interpretation was required. For this reason, an approach that is better described as 'thematic synthesis' (Thomas and Harden, 2008) was used. Figure 4 shows the steps involved.

Figure 4. Steps used in the thematic synthesis of included studies

1. Reading and re-reading of included papers to acquire a sense of the studies as a whole
2. Coding of text line-by-line
3. Extraction of all relevant primary data and author interpretations from all included papers (see 'Extraction') with an accompanying critical appraisal assessment (see 'Critical appraisal') for each paper
4. Condensing of similar study findings (first level constructs) into descriptive themes (second level constructs): a stage of interpretation that remains 'close' to the primary studies
5. Generation of analytical themes: a stage of interpretation in which the reviewers 'go beyond' the primary studies and generate new interpretive constructs, explanations or hypotheses – that is, theory about the importance of treatment outcomes

ASSESSMENT OF CONFIDENCE IN REVIEW FINDINGS

In assessing the *overall* quality of review findings (that is, determining the degree of confidence that should be placed in the findings of a qualitative synthesis), this project shall trial the emerging CERQual methodology. Similar to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach for effectiveness reviews, CERQual – or the Confidence in the Evidence from Reviews of Qualitative research approach – is an attempt to apply a coherent and transparent assessment of the "extent to which a review finding is a reasonable representation of the phenomenon of interest" (Lewin *et al.*, 2015). Such evaluations enable the end-user of a review to determine the degree of importance to assign to a particular review finding.

"[CERQual] is not attempting to produce a rigid checklist to appraise review findings—the risks of applying such critical appraisal checklists unreflectively to qualitative primary studies have been discussed widely in the literature. Rather, CERQual is conceived of as a structured approach to appraisal that requires reviewer judgement and interpretation throughout the approach." (Lewin et al*., 2015)*

The components of a CERQual analysis "reflect similar concerns to the elements included in the GRADE approach for assessing the certainty of evidence on the effectiveness of interventions. However, CERQual considers these issues from a qualitative perspective." (Lewin *et al.*, 2015) The 4 components of a CERQual assessment are: methodological limitations (determined using the CASP critical appraisal assessments, as described above), relevance, coherence and adequacy of data; see Table 5 for an explanation of each.

Table 5. Framework for CERQual assessment (adapted from Lewin *et al.* (2015))

Component	***Description***
Methodological limitations	The extent to which there are problems in the design or conduct of the primary studies that contributed evidence to the review finding
Relevance	The extent to which the body of evidence from the primary studies supporting a review finding is applicable to the context (perspective or population researched, the phenomenon of interest or the setting) specified in the review question
Coherence	The extent to which the review finding is well grounded in data from the contributing primary studies and provides a convincing explanation for the patterns found in these data
Adequacy of data	An overall determination of the degree of richness (detail contributing to an understanding of the phenomenon of interest) and quantity of data supporting a review finding

Each of these 4 components are assigned a degree of concern, based on the reviewer's assessment: severe concerns, moderate concerns, mild concerns or no concerns. They are then judged together, as a body of evidence, to give an overall assessment of confidence in the review finding. There are 4 levels of confidence: high, moderate, low and very low (see Table 6 for an explanation of each).

There "is no hierarchy of evidence among methodologies for qualitative studies" (Joanna Briggs Institute, 2014), so all review findings begin as 'high confidence'. Based on the concerns raised for each domain of the CERQual framework, the confidence was adjusted by the reviewer. This phase of the process is not well defined in the CERQual literature, so the

reviewer developed a scoring system by which to systematically and consistently quantify the value judgements involved. From a starting score of 12, points were removed for the concerns detailed in each domain: -3 for severe concerns, -2 for moderate concerns, -1 for mild concerns. The overall confidence was determined as follows: for an aggregate score of 11 to 12, there is high confidence that the review finding is a reasonable representation of the phenomenon of interest; 8 to 10, moderate confidence; 5 to 7, low confidence; 1 to 4, very low confidence. These judgments are quantitatively (with regards the CERQual scores) and qualitatively substantiated within the CERQual profiles (see Table ***).

Table 6. Levels of confidence in a review finding (adapted from Lewin *et al.* (2015))

Level	***Aggregate score***	***Description***
High confidence	11 to 12	It is highly likely that the review finding is a reasonable representation of the phenomenon of interest
Moderate confidence	8 to 10	It is likely that the review finding is a reasonable representation of the phenomenon of interest
Low confidence	5 to 7	It is possible that the review finding is a reasonable representation of the phenomenon of interest
Very low confidence	1 to 4	It is not clear whether the review finding is a reasonable representation of the phenomenon of interest

COMPARISON TO CURRENT CLINICAL EFFECTIVENESS RESEARCH

To parameterise the potential value of the qualitative evidence synthesis conducted, the outcomes identified as significant within the review will be compared to those in clinical effectiveness reviews. The aim is to investigate the inclusion of outcomes identified as important to patients in the current evidence base, and identify if there is a need for future antituberculosis treatment effectiveness research to consider more patient-centred outcomes

First, the outcomes identified as significant will be compared against those outcomes selected for reporting in Cochrane systematic reviews of treatment for active TB, and secondly within the primary papers included within these reviews.

Table 7. Search strategies for the retrieval of Cochrane reviews of TB treatment

Database	***Search terms***	***Other limits***	***Date***	***Retrievals***

Cochrane Database of Systematic Reviews	Tuberculosis OR 'TB'	Cochrane reviews and 'other reviews' English language Interventions: pharmacological treatment for active TB Population: people with active TB without comorbidities or coexisting conditions that might affect the experience or management of their TB	Up to 10th December 2015	79

The Cochrane Database of Systematic Reviews was searched using a simple strategy of TB terms (Tuberculosis OR 'TB') to pull in all Cochrane reviews and 'other reviews' of published in English (see Table 7 for further details of the search strategy). The identified papers were then screened to ensure that the population of interest was people with active TB who did not have comorbidities or coexisting conditions that might affect the experience or management of their TB, and that the review was of antituberculosis drug treatment.

The outcomes identified in the systematic review of patient perspectives on TB and management will then be compared against those included in the latest NICE guidance for the treatment of TB (NICE, 2016), for which this reviewer conducted the systematic reviews of antituberculosis treatment. The outcomes will also be compared against those reported in the primary studies included within the NICE reviews.

EXAMINING THE VOLUME AND DIVERSITY OF PATIENT PERSPECTIVES INCLUDED

It is the hypothesis of this research project that qualitative systematic reviews have the potential to increase the volume, depth and diversity of stakeholder – specifically patient – perspectives that might be considered in a particular decision; in this case, in the development of a core outcome set for TB.

The volume and diversity of perspectives pooled within the qualitative systematic review of patient perspectives on TB and it treatment will be compared against that for the COS recorded as having included qualitative studies in patients in their development on the COMET Initiative database (available at: http://www.comet-initiative.org/studies/search). To ensure that all papers describing COS development that incorporated patient perspectives were included, the database was filtered by the stakeholder involved: studies that were indexed as 'consumers (patients)' and 'service users' were included. The other stakeholder indexing terms were not considered relevant to patients. Furthermore, to ensure that only published studies were retrieved, the database was additionally filtered by publication year: studies that were published during or before 2015 were included (i.e. any paper that had been published at any time). Only

studies using qualitative methods to gather patient perspectives were ultimately included; surveys were explicitly excluded from this analysis as they are considered to be quantitative social research methods. See Table 8 below for full details of the search strategy.

Table 8. Search strategies for the retrieval of papers describing COS development incorporating patient perspectives

Database	*Filters applied*	*Other limits*	*Date*	*Retrievals*
COMET Initiative database	Stakeholder involved: • 'consumers (patients)' • 'service users'	Qualitative studies English language Publication year: up to and including 2015	Up to 10th December 2015	65

Papers were excluded from the analysis if patient perspectives were gathered solely using quantitative social research methods (surveys, for example). Although these are useful in gaining the views of a large number of patients and may be particularly useful in validating outcome sets across a broad patient group, they do not generate 'rich' data which is desirable during the development phase of a COS. The purpose of this analysis was to increase the volume *and depth* of the patient perspectives used in COS development, as well as the diversity of the population used to do this, and therefore survey-based studies were not used in the comparison.

The number of patients included in qualitative research studies within the development of each COS (at the level of the disease area, not at the individual study) was compared to the pooled sample size within the present qualitative evidence review. The diversity of the populations included was also compared on the basis of geographical location, including the level of TB incidence, as well as age, gender and socioeconomic characteristics.

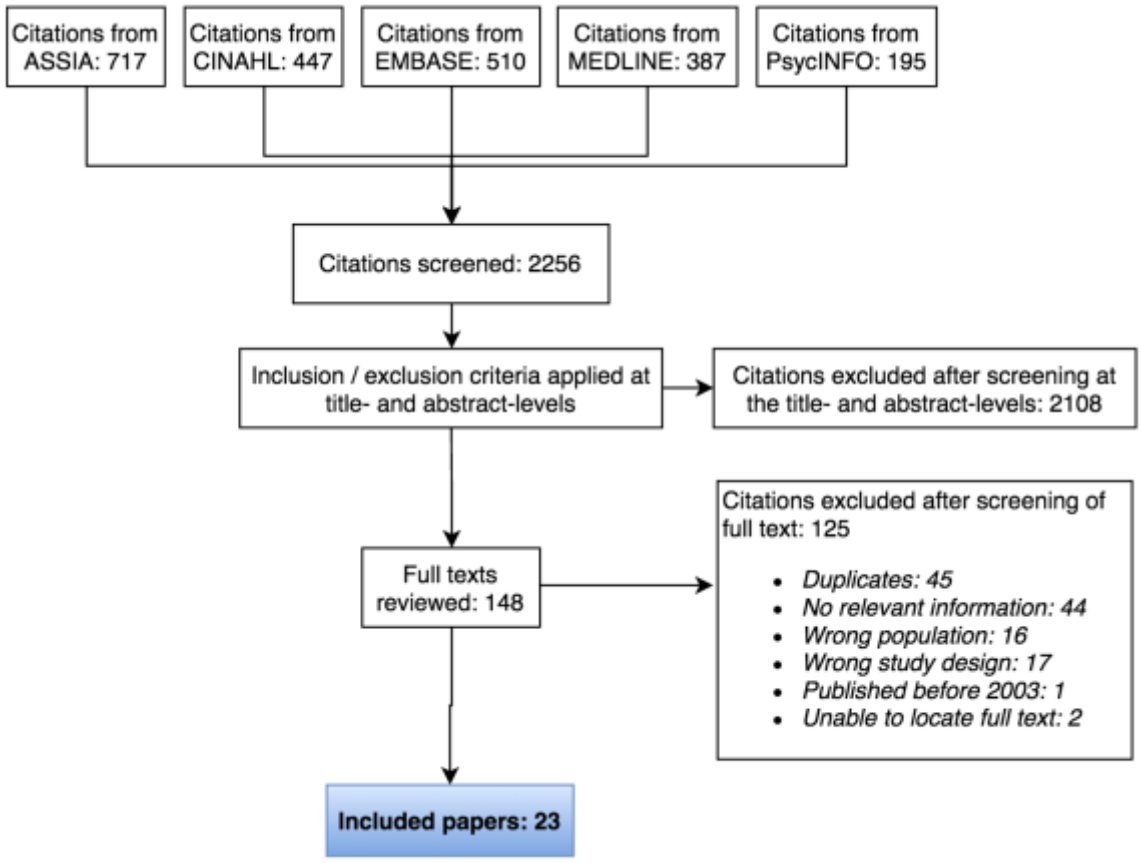
REPORTING STANDARDS

This project is reported in accordance with the Enhancing transparency in reporting the synthesis of qualitative research (ENTREQ) guidelines (Tong *et al*., 2012).

RESULTS OF LITERATURE SEARCHES

ASSIA, CINAHL, Embase, MEDLINE, and PsycINFO were searched using broad strategies of TB and qualitative research terms (indexed and free text) (see 'The literature search' above for more details). ASSIA yielded 717 articles; full texts were retrieved for 12, and after exclusions 3 were included. CINAHL yielded 447 articles; full texts were retrieved for 43, and after exclusions 12 were included. Embase yielded 510 articles; full texts were retrieved for 28, and after exclusions 7 were included. MEDLINE yielded 387 articles; full texts were retrieved for 16, and after exclusions 8 were included. And finally, PsycINFO yielded 195 articles; full texts were retrieved for 49, and after exclusions 10 were included. See Figure 5 and Appendix A for further details.

Figure 5. PRISMA flow diagram of study inclusion and exclusion process



The references and footnotes of included papers were examined for other possible inclusions, though none were ultimately included. 2 papers were identified through personal knowledge, though again neither were ultimately included. The lack of directly relevant studies identified during scoping and through the course of the searching meant that there were no authors that were known to be experts in the field who could be contacted.

INCLUDED STUDIES

Overall, after duplications were accounted for, 23 papers describing 22 studies were included (Acha *et al.*, 2007; Bennstam *et al.*, 2004; Cramm *et al.*, 2010; Dias *et al.*, 2013; Franck *et al.*, 2014; Gerrish *et al.*, 2012; Gerrish *et al.*, 2013; Hu *et al.*, 2008; Khan, 2012; Mafigiri *et al.*, 2012; Naidoo *et al.*, 2009; Paz and Sá, 2009; Paz-Soldan *et al.*, 2013; Queiroz *et al.*, 2012; Reyes-Guillen *et al.*, 2008; Rundi, 2010; Sagbakken *et al.*, 2008; Tadesse *et al.*, 2013; Van den Boogaard *et al.*, 2012; Van Elsland *et al.*, 2012; Xu *et al.*, 2009; Zhang *et al.*, 2010; Zuñiga *et al.*, 2014).

The analysis synthesises findings from primary qualitative research conducted across 13 countries: 5 in Sub-Saharan Africa, 3 in Asia, 2 in South America, 1 in Central America, 1 in North America and 1 in Europe. Patient population sizes ranged from 4 to 107, though 1 study did not report the population size and 12 included other types of participants (healthcare workers, carers, relatives of patients, community leaders and other members of the studied community. Most studies included both men and women, and there was a spread of age groups. See 'The volume, depth and diversity of patient perspectives included' for further examination of the included population.

None of the studies were conducted specifically with the aim of examining patient views on treatment outcomes or their prioritisation. The primary phenomena studied included determinants of treatment compliance, TB-related stigma, gender variations in experience, psychosocial support, and experiences of TB diagnosis and treatment more broadly. The methods employed were not consistently – or, in many cases clearly – reported, but study designs included participant observation, focus groups and interviews (with both semi-structured and open-ended questions) and Q-methodology. Analyses suffered from similarly opaque reporting, were described variously as thematic coding, content analysis, grounded theory, phenomenal analysis, framework approaches and discourse analysis.

REVIEW FINDINGS

Based on the initial coding, 19 broad, descriptive themes (second level constructs) were developed from the relevant data and author interpretations within the included studies (first level constructs). Each theme was further analysed and aggregated – using a thematic

synthesis approach – to produce 5 overarching analytical themes. These 'third level constructs' emerged as generated knowledge about TB treatment outcomes that were significant to patients: improvement in the signs and symptoms of disease; mortality and survival; treatment failure, success and cure; the adverse effects of treatment; and the overall impact of TB and its management on patients' ability to 'function'. See 'A systematic review of patient perspectives on tuberculosis treatment outcomes' for further information on how these findings were derived from the literature.

The CERQual assessments of confidence for each of the review findings (that is, the confidence that each review finding is a reasonable representation of the phenomenon of interest) – based upon an assessment of the methodological limitations, relevance, coherence and adequacy of the data underpinning each finding – ranged from moderate to very low, though the majority of findings were graded as low. See 'Assessment of confidence in review findings' for further information on the CERQual process.

A summary of the findings is available in Table 9. The full tables of qualitative findings, which contain all the constituent primary study data and the full CERQual profiles are available at the end of this chapter, in Tables 10 and 11.

Table 9. Summary of qualitative systematic review findings

Review findings	*Number of studies*	*Confidence in the review finding*
Improvement in the signs and symptoms of disease	**9**	**Low to very low**
The physical and psychological impact of the symptoms of TB, and the relief felt when symptoms were alleviated, featured consistently in patients' narratives about their experiences of the disease.	4	Low • methodological limitations: moderate • concerns about relevance: severe • concerns about coherence: none • concerns about adequacy: moderate
Antituberculosis treatment was viewed as a way to relieve the symptoms of the disease, which motivated patients to both adhere to and/or complete their treatment regimens.	4	Very low • methodological limitations: moderate • concerns about relevance: severe • concerns about coherence: mild • concerns about adequacy: moderate
Symptom relief seems to have additional significance as a surrogate - or even sign of hope - for recovery and survival. This link to recovery and survival appears to further bolster the motivation that symptom relief provides to adhere to and complete treatment.	2	Very low • methodological limitations: moderate • concerns about relevance: severe • concerns about coherence: mild • concerns about adequacy: severe
Mortality and survival	**5**	**Low**

Patients with TB reported fear of dying as a source of suffering.	3	Low • methodological limitations: moderate • concerns about relevance: moderate • concerns about coherence: none • concerns about adequacy: mild
Tuberculosis was viewed as a "deadly disease" and antituberculosis treatment as a "way to stay alive and healthy", which motivated patients to both adhere to and/or complete their treatment regimens. The possibility that that they might die from their disease caused patients to enact positive health behaviours.	3	Low • methodological limitations: moderate • concerns about relevance: severe • concerns about coherence: mild • concerns about adequacy: mild
Treatment failure, success and cure	**10**	**Low**
Many patients doubted that treatment will cure their disease completely.	7	Low • methodological limitations: moderate • concerns about relevance: severe • concerns about coherence: mild • concerns about adequacy: none
Antituberculosis treatment was viewed as a "way to stay alive and healthy", which motivated patients to both adhere to and/or complete their treatment regimens.	5	Low • methodological limitations: moderate • concerns about relevance: severe • concerns about coherence: mild • concerns about adequacy: mild
Adverse effects of treatment	**12**	**Low**

The adverse effects of regimens featured consistently in patients' narratives about the burden of treatment.	4	Low • methodological limitations: moderate • concerns about relevance: moderate • concerns about coherence: none • concerns about adequacy: mild
Patients reported that the adverse effects experienced "could be as severe or more severe" than the disease itself.	2	Low • methodological limitations: moderate • concerns about relevance: severe • concerns about coherence: none • concerns about adequacy: moderate
The adverse effects of the antituberculosis drugs was a barrier both to patients adhering to their treatment regimens and to the completion of the full treatment period. The physical, psychological and social burden of the adverse effects of treatment (see above) made patients "want to give up".	5	Low • methodological limitations: moderate • concerns about relevance: severe • concerns about coherence: none • concerns about adequacy: none
There was concern amongst some patients that the physical impact of the adverse effects of treatment regimens may stretch far beyond the end of treatment or cure of the disease, and may have long-term consequences in terms of their ability to function and, beyond that, to flourish.	2	Low • methodological limitations: moderate • concerns about relevance: severe • concerns about coherence: none • concerns about adequacy: moderate

In addition to the physical experience, patients reported psychosocial impacts arising from the adverse effects of treatment regimens.	4	Low • methodological limitations: moderate • concerns about relevance: severe • concerns about coherence: none • concerns about adequacy: mild
For those on the more intensive regimens necessitated by drug-resistant disease, the psychological impact of adverse effects even extended to suicidal ideation.	1	Low • methodological limitations: moderate • concerns about relevance: moderate • concerns about coherence: none • concerns about adequacy: severe
Impact on functioning	**9**	**Moderate to very low**
Patients reported a range of limitations – social, physical, developmental, educational, economic – to their ability to function. These was imposed both by the treatment of their TB and by the disease itself, and affected their wellbeing and their ability to 'flourish'.	9	Moderate • methodological limitations: moderate • concerns about relevance: moderate • concerns about coherence: none • concerns about adequacy: none
There was concern that the treatment of TB or the disease itself may have an impact on the education and development of children and young people affected.	2	Low • methodological limitations: moderate • concerns about relevance: moderate • concerns about coherence: none • concerns about adequacy: moderate

Patients reported that the treatment of TB and the effects of disease itself affected their ability to work. In addition to the loss of wages that this is associated with, as well as the subsequent financial hardship, patients described "feelings of 'uselessness' and being 'a burden' on their already struggling families."	3	Low • methodological limitations: moderate • concerns about relevance: moderate • concerns about coherence: none • concerns about adequacy: moderate
Patients reported social impacts from the treatment and experience of disease. Some experienced feelings of social isolation (an isolation perhaps compounded by discrimination arising from the disease itself) because they lacked energy to join in with social activities, such as playing sports or drinking, or simply no longer felt like going out in public, making it difficult to maintain relationships.	3	Very low • methodological limitations: moderate • concerns about relevance: severe • concerns about coherence: moderate • concerns about adequacy: moderate
The significance of 'cure' - in addition to its inherent desirability as a "way to stay alive and healthy" - was further enacted as a 'gatekeeper' to patients' returning to normal functioning, and even the possibility that they might "flourish".	3	Low • methodological limitations: moderate • concerns about relevance: moderate • concerns about coherence: mild • concerns about adequacy: mild
The importance of adherence is also enacted as a 'gatekeeper', first to cure, then (as described above) to patients' returning to normal functioning, and even the possibility that they might "flourish".	2	Low • methodological limitations: moderate • concerns about relevance: moderate • concerns about coherence: mild • concerns about adequacy: moderate

IMPROVEMENT IN THE SIGNS AND SYMPTOMS OF DISEASE

The physical and psychological impact of the symptoms of TB – and the relief that was felt when symptoms were alleviated – featured consistently in patients' narratives about their experiences of the disease, although these was generally spoken of in a broad, nonspecific way (Mafigiri *et al*., 2012; Queiroz *et al.*, 2012; Reyes-Guillen *et al*., 2008; Zuñiga *et al*., 2014).

The signs and symptoms of disease described by patients included weight loss, pain and cough. For example, Reyes-Guillen *et al*. (2008) reported that patients' main concerns included a belief that "treatment didn't get rid of the cough", and Zuñiga *et al*. (2014) noted that,

> *"Weight loss was seen as a very negative side effect of TB. Several participants talked about being skinny and how horrible they looked. Five participants reported weight loss, some lost up to 40 pounds, and how much they had gained weight back since receiving treatment."*

There were moderate methodological concerns for this finding, predominantly arising from poor reporting. This related to the treatment regimens used, the relationship between researcher and participants, sampling approach and data analysis, but also a lack of patient quotes for the relevant author's statements.

There were also severe concerns about relevance. In addition to no study having been designed to directly examine the prioritisation of treatment outcomes (which is applicable across the review findings and evidence base), the relevance of the study populations was limited by the presence of comorbidities that may affect the experience and management of TB: HIV, kidney disease and liver disease.

There were moderate concerns about the adequacy of the data due to the data not sufficiently reflecting the international and diverse patient group that a COS would apply to.

Overall confidence in the review finding was low.

Antituberculosis treatment was viewed as a way to relieve the symptoms of the disease, which motivated patients to both adhere to and/or complete their treatment regimens (Cramm *et al*., 2010; Naidoo *et al*., 2009; Tadesse *et al*., 2013; Van den Boogaard *et al*., 2012). For example, one patient reported that,

> *"TB made me really sick. After I took the pills, I felt better again. When I take my pills for a few months, I am cured from TB. That is why I am going to finish my treatment." (patient quote; Cramm* et al*., 2010)*

And another,

> *"For sure, the pain that I had, the way it has been relieved, I need to continue taking the medication." (patient quote; Van den Boogaard* et al*., 2012)*

Again, there were moderate methodological concerns for this finding, again arising from poor reporting. There were severe concerns regarding the relevance of the finding, again due to the divergence of the phenomena of interest in the studies from those of the review and to the inclusion of people with HIV in the study populations. There were, again, moderate concerns about the adequacy of the data due to the data not sufficiently reflecting the international and diverse patient group that a COS would apply to.

There were mild concerns about coherence because other statements demonstrated a lack of trust in the capability of treatment to make them healthy again, particularly in those experiencing side effects from the treatment. However, it is perhaps not surprising that such conflicts exist given the difficulties experienced by many and the 'high stakes' of their situation – TB can kill if left untreated and, where it does not kill, it can have long-term impacts on morbidity and functioning.

The overall confidence in the review finding was very low.

The relief of patients' symptoms seems to have additional significance as a surrogate or even a sign of hope for recovery and survival. This link to recovery and survival appears to further bolster the motivation that symptom relief provides to adhere to and complete treatment. For example,

> *"You go to the Health Center every day to check your weight. If it's not higher than last time, you will ask yourself why and be afraid that your treatment will not bring recovery. You will ask yourself: Will I recover or die? Other people will still be afraid of him, they will still fear to get TB from him. They are afraid: Will he recover or not from his TB? If you get TB, it's very bad . . . it might happen that you will not recover." [patient quote; Bennstam, 2004]*

See 'The interconnection between symptom relief, mortality, cure and the impact of treatment on functioning' below for further details about this phenomenon, including a discussion of the CERQual assessment.

Taken together, these findings were synthesised to give the treatment outcome of 'improvement in the signs and symptoms of disease'. The overall confidence that this outcome is an outcome of importance to patience is low to very low.

MORTALITY AND SURVIVAL

Patients with TB reported a fear of dying to be a source of suffering (Dias *et al.*, 2013; Gerrish *et al.*, 2012; Zhang *et al.*, 2010). In some studies, this was a fear felt by the patients themselves, with that fear bringing about suffering through distress or self-stigma:

> *"'At the news that I was diagnosed with PTB, I was badly fearful. When I was a child, I often heard that if one suffered from it…he would die.' (Male, 20 years old, continuation phase, outpatient)" (Zhang* et al*., 2010)*

In other studies, this was a fear on the part of other people, with the fear bringing about suffering for the patient through stigma or discrimination.

Again, there were moderate methodological concerns for this finding, again arising from poor reporting. There were moderate concerns regarding the relevance of the finding, again due to the divergence of the phenomena of interest in the studies from those of the review and to the inclusion of people with HIV in the study populations. There were, again, concerns about the adequacy of the data due to the data not sufficiently reflecting the international and diverse patient group that a COS would apply to, though less so than for other findings. Therefore, the overall confidence in the review finding was low.

> *"Because when we'd hear about tuberculosis, it was said to be a deadly disease … I felt that I had to do my very best not to skip a single day of treatment." (patient quote; Dias* et al*., 2013)*

Tuberculosis was viewed as a "deadly disease" and antituberculosis treatment as a way to stay alive, which motivated patients to both adhere to and/or complete their treatment regimens, to enact positive health behaviours (Dias *et al.*, 2013; Van den Boogaard *et al.*, 2012). However, there was some evidence to mitigate the strength of this finding: patients deemed to have complied with their medication in one study rated the chance of dying from TB of low importance in their motivation for adhering to treatment (Cramm *et al.*, 2010).

Poor reporting of methods and a lack of patient quotes again led to moderate methodological concerns for this finding. There were severe concerns regarding the relevance of the finding, again due to the divergence of the phenomena of interest in the studies from those of the review and to the inclusion of people with HIV in the study populations. There were mild concerns about coherence for reasons equivalent to those noted above: because other statements demonstrated a lack of trust in the capability of treatment to to keep them alive. However, again, it is perhaps not surprising that such conflicts exist given the difficulties experienced by many and the 'high stakes' of their situation.

Although data felt rich in the varied descriptions of the phenomena and was indirectly supported by other findings, it came from just 3 studies, conducted in 4 countries (1 South America, 2 Africa). There were few, if any, children included, and patients were all from poorer settings. For these reasons, there were again mild concerns about the adequacy of the data: it did not sufficiently reflect the international and diverse patient group that a COS would apply to.

The overall confidence in the review finding was low.

Taken together, these findings were synthesised to give the treatment outcome of 'mortality and survival'. The overall confidence that this outcome is an outcome of importance to patience is low.

TREATMENT FAILURE, SUCCESS AND CURE

> *"It is impossible for a TB patient to get completely cured. … Once a person gets infected, the disease will keep resurfacing." (patient quote; Khan, 2012)*

Many patients doubted that treatment will cure their disease completely (Acha *et al.*, 2007; Gerrish *et al.*, 2013; Khan, 2012; Mafigiri *et al.*, 2012; Reyes-Guillen *et al.*, 2008; Van den Boogaard *et al.*, 2012; Zhang *et al.*, 2010). This skepticism – or fear – came from a number of causes, including 'hearsay' or misinformation around the disease, the long duration of treatment required for recovery, and knowledge or personal experience of treatment failure in the past, as well as a degree of distrust in biomedicine and a perceived "incurability" of stigma, even if cure was achieved clinically. Other studies reported that all participants believed that TB is curable, citing the converse of the reasons provided above. This does not, however, limit the potential importance of cure as treatment outcome for these patients.

Again, antituberculosis treatment was viewed as a way to stay healthy, which motivated patients to both adhere to and/or complete their treatment regimens (Cramm *et al.*, 2010; Hu *et al.*, 2008; Mafigiri *et al.*, 2012; Naidoo *et al.*, 2009; Van den Boogaard *et al.*, 2012). For example,

> *"TB made me really sick. After I took the pills, I felt better again. When I take my pills for a few months, I am cured from TB. That is why I am going to finish my treatment." (patient quote; Cramm* et al.*, 2010)*

Knowing of another person who had been cured further supported this motivation, and to some patients this motivation to be cured and recover made measures such as the direct observation of therapy unnecessary, even wasteful:

> *"It's not necessary. I have self-consciousness; I don't want to waste their time, they are so busy. I should be responsible to myself, because I want to recover." (patient quote; Hu et al., 2008)*

Poor reporting of methods and a lack of patient quotes again led to moderate methodological concerns for both of these findings. There were severe concerns regarding the relevance of the finding, again due to the divergence of the phenomena of interest in the studies from those of the review and to the inclusion of people with HIV in the study populations. There were mild concerns about coherence because statements were also identified that showed belief that antituberculosis treatment was as a way to make them healthy again and to keep them alive; however, as stated previously, it is perhaps not surprising that such conflicts exist given the difficulties experienced by many and the 'high stakes' of their situation.

Although data felt rich in the varied descriptions of the phenomena, and was indirectly supported by other findings, there were mild concerns about adequacy for the finding that the view of treatment as a means of staying healthy motivated patients to adhere to treatment. This was because it did not sufficiently reflect the international and diverse patient group that a COS would apply to. It came from studies conducted in just 4 countries (primarily in Sub-Saharan Africa, with just 1 conducted outside of the region (in China), there were very few children included, and patients were all from poorer settings.

For the reasons described above, the overall confidence in these findings was low.

Taken together, these findings were synthesised to give the treatment outcome of 'treatment failure, success and cure'. The overall confidence that this outcome is an outcome of importance to patience is low.

ADVERSE EFFECTS OF TREATMENT

Alongside the long duration of treatment and the high pill burden, the adverse effects of regimens featured consistently in patients' narratives about the burden of treatment (Acha et *al*., 2007; Franck *et al*., 2014; Paz and Sá, 2009; Van Elsland *et al*., 2012). Nausesa, vomitting, stomach pain, joint pain, dizzyness, and weakness were common. Other side effects mentioned include weight gain, skin rashes and behavioural changes (motor restlessness and aggression). One study also reported that a darkening of the skin pigmentation reported to be caused by clofazamine was a particularly burdensome side effect of the treatment due to the "negative attitudes towards darker skin colour in Peruvian culture", further compounded by the stigma already felt because of their disease (Acha *et al.*, 2007).

Poor reporting of methods and a lack of patient quotes again led to moderate methodological concerns for this finding. There were moderate concerns regarding the relevance of the finding, again due to the divergence of the phenomena of interest in the studies from those of the review and to the possible inclusion of people with HIV in the study populations. There were, again, mild concerns about the adequacy of the data due to the data not sufficiently reflecting the international and diverse patient group that a COS would apply to:

although the data felt rich in the varied descriptions of the phenomena, it came from just 4 studies, conducted primarily in urban settings in only 4 countries. The overall confidence in the review finding was low.

Some patients reported that the adverse effects experienced "could be as severe or more severe" than the disease itself (Reyes-Guillen *et al*., 2008; Zuñiga *et al*., 2014). Poor reporting of methods and a lack of patient quotes again led to moderate methodological concerns for this finding. There were severe concerns regarding the relevance of the finding due to the divergence of the phenomena of interest in the studies from those of the review and to the inclusion of people with HIV in the study populations. There were moderate concerns about the adequacy of the data due to the data not sufficiently reflecting the international and diverse patient group that a COS would apply to: data was descriptively 'thin' and came from just 2 studies, both conducted in or around Mexico. The overall confidence in the review finding was low.

The adverse effects of the antituberculosis drugs were a barrier both to patients adhering to their treatment regimens and to the completion of the full treatment period (Franck *et al*., 2014; Paz and Sá, 2009; Tadesse *et al*., 2013; Xu et *al*., 2009; Zuñiga *et al*., 2014). The physical, psychological and social burden of the adverse effects of treatment (see above) made patients 'want to give up':

> *"When I take the medication I feel sick, get weak and feel just like lying. At the beginning it was worse because I got sickness, stomach ache, vomiting, but then it all passed. Now, I only have back pain and tiredness, but they told me it is like this, I have to be patient 'cause it'll get better. I almost can't close my hands because of my joint pain, sometimes I feel like stopping the medication, but I think about my family, myself and keep going, but I'm getting better." (patient quote; Paz and Sá, 2009)*

There were moderate methodological concerns for this finding because of the poor reporting of methods and a lack of patient quotes. There were severe concerns regarding the relevance of the finding due to the divergence of the phenomena of interest in the studies from those of the review and to the inclusion of people with comorbidities that might affect the experience of disease or its management. The overall confidence in the review finding was graded as low.

There was concern amongst some patients that the physical impact of the adverse effects of treatment regimens may stretch far beyond the end of treatment or cure of the disease, and may have long-term consequences in terms of their ability to function and, beyond that, to flourish (Zhang et al., 2010; Zuñiga et al., 2014). For example,

"It is said that taking anti-TB drugs might lower fertility, I am rather worried about it." (patient quote; Zuñiga et al., 2014)

Poor reporting of methods and a lack of patient quotes again led to moderate methodological concerns for this finding. Again, there were severe concerns regarding the relevance of the finding due to the divergence of the phenomena of interest in the studies from those of the review and to the inclusion of people with comorbidities in the study populations. There were moderate concerns about the adequacy of the data due to its thinness, although it was indirectly supported by other findings, and the fact that the data was not felt to sufficiently reflect the international and diverse patient group that a COS would apply to. Additionally, it came from just 2 studies conducted in poorer settings, sampling adults only. The overall confidence in the review finding was low.

In addition to the physical experience of the adverse effects of treatment regimens, patients reported psychosocial impacts (Acha *et al.*, 2007; Paz-Soldan *et al*., 2013; Sagbakken *et al*., 2008; Van den Boogaard *et al*., 2012). This manifested in a number of ways. For example, for some the adverse events of their treatment led to feelings of social isolation (an isolation perhaps compounded by discrimination arising from the disease itself) because patients no longer felt able to join in with social activities, such as playing sports or drinking, or simply no longer felt like going out in public. For others, adverse effects such as hunger, or the need to consume their antituberculosis drugs with high-protein foods foods in order to reduce the risk or severity of adverse effects, "served as a continuous reminder of their poverty" (Sagbakken *et al*., 2008) and "aggravated the perceived socioeconomic difficulties that participants had to cope with" (Van den Boogaard *et al*., 2012).

For those on the more intensive regimens necessitated by drug-resistant disease, the psychological impact of adverse effects even extended to suicidal ideation:

"All of us go through that (suicidal ideation); that's normal. The beginning of treatment is so hard, but it gets easier. I thought about killing myself many times. The side effects were so bad; I was so depressed. Treatment seemed like an eternity. But little by little, things got better." (patient quote; Acha et al., 2007)

Poor reporting of methods and a lack of patient quotes again led to moderate methodological concerns for this finding. Again, there were severe concerns regarding the relevance of the finding due to the divergence of the phenomena of interest in the studies from those of the review and to the inclusion of people with HIV. There were mild concerns about the adequacy of the data due to the data not sufficiently reflecting the international and diverse patient group that a COS would apply to, and severe concerns relating to the extension of the psychological impact of adverse effects to suicidal ideation because this finding arose from just a single study. The overall confidence in this review finding was low.

Taken together, these findings were synthesised to give the treatment outcome of 'adverse effects of treatment'. The overall confidence that this outcome is an outcome of importance to patience is low.

IMPACT ON FUNCTIONING

> *"I was very ill. It is everything to get back to normal life, to feel fit and strong. It took three years to get back to normal." (patient quote; Gerrish* et al*., 2013)*

Patients reported a range of limitations – social, physical, developmental, educational, economic – to their ability to function (Acha *et al.*, 2007; Franck *et al.*, 2014; Gerrish *et al.*, 2013; Hu *et al.*, 2008; Paz-Soldan *et al.*, 2013; Queiroz *et al.*, 2012; Reyes-Guillen *et al.*, 2008; Rundi, 2010; Zhang *et al.*, 2010). These was imposed both by the treatment of their TB and by the disease itself, and affected their wellbeing and their ability to 'flourish'.

The overall confidence in this broad review finding was moderate. There were no concerns about the adequacy or coherence of the data, though there were moderate methodological concerns (arising from a lack of information relating to study design) and moderate concerns about relevance (no study was designed to directly examine the prioritisation of treatment outcomes and the inclusion of a number of people with HIV).

There was concern that the treatment of TB or the disease itself may have an impact on the education and development of children and young people affected (Acha *et al.*, 2007; Franck *et al.*, 2014). For example, Franck *et al*. (2014) reported that,

> *"Adverse effects are highly disruptive, producing little incentive for children to remain adherent to treatment. Furthermore, medications frequently produce acute academic disruptions, sometimes persisting beyond the termination of treatment. In particular, some children may be at higher risk of experiencing cognitive treatment-related adverse effects, including various psychiatric disorders."*

Again, there were moderate methodological concerns for this finding, again arising from poor reporting. There were moderate concerns regarding the relevance of the finding because of the divergence of the phenomena of interest in the studies from those of the review and to the possible inclusion of people with HIV in the study populations. There were moderate concerns about the adequacy of the data due to the small amount of data underpinning it and a lack of 'richness' in the descriptions of the phenomena. For these reasons, the overall confidence in the review finding was low.

Patients also reported that the treatment of TB and the disease itself affected their ability to work (Acha *et al.*, 2007; Gerrish *et al.*, 2013; Reyes-Guillen *et al.*, 2008). In addition to the loss of wages that this is associated with, as well as the subsequent financial hardship, patients described "feelings of 'uselessness' and being 'a burden' on their already struggling families" (Acha *et al.*, 2007). However, there was some evidence to mitigate the strength of this finding: patients deemed to have complied with their medication in one study rated the possible loss of wages of low importance in their motivation for adhering to treatment (Cramm *et al.*, 2010).

Poor reporting again led to moderate methodological concerns for this finding. There were moderate concerns regarding the relevance of the finding because of the divergence of the phenomena of interest in the studies from those of the review and to the possible inclusion of people with HIV in the study populations. There were moderate concerns about the adequacy of the thinness of the data and the small number of studies in which it was noted. It was also felt that the data did not sufficiently reflect the diverse patient group that a COS would apply to (there were few, if any, children included, and patients were all from poorer settings). Therefore, the overall confidence in the review finding was low.

Patients reported social impacts from the treatment and experience of disease. Some experienced feelings of social isolation (an isolation perhaps compounded by discrimination arising from the disease itself) because they lacked energy to join in with social activities, such as playing sports or drinking, or simply no longer felt like going out in public, making it difficult to maintain relationships. For example,

> *"Others mentioned that the medications made them feel so queasy and tired that they no longer felt like going out in public. A number of TB positive men, for example, mentioned that they used to play soccer and then drink beer with their friends, but during treatment had no energy for soccer and were not allowed to drink alcohol, so as a result they saw their friends significantly less." (Paz-Soldan* et al*., 2013)*

Again, poor reporting again led to moderate methodological concerns for this finding. There were severe concerns regarding the relevance of the finding because of the divergence of the phenomena of interest in the studies from those of the review and to the inclusion of people with HIV in the study populations. There were moderate concerns about coherence because other statements were identified that suggested friends and family were supportive, mitigating against the withdrawal of patients from social networks. There were moderate concerns about the adequacy of the data due to the small amount of number of studies in which it was noted and due to the data not sufficiently reflecting the international and diverse patient group that a COS would apply to. Therefore, the overall confidence in the review finding was very low.

Taken together, these findings were synthesised to give the treatment outcome of 'impact on functioning'. The overall confidence that this outcome is an outcome of importance to patience is low.

THE INTERCONNECTION BETWEEN SYMPTOM RELIEF, MORTALITY, CURE AND THE IMPACT OF TREATMENT ON FUNCTIONING

Beyond the significance as an outcome of treatment in its own right, symptom relief seems to have additional significance as a surrogate – or even sign of hope – for recovery and survival (Bennstam *et al.*, 2004; Cramm *et al.*, 2010). This link to recovery and survival appears to further bolster the motivation that symptom relief provides to adhere to and complete treatment.

> *"You go to the Health Center every day to check your weight. If it's not higher than last time, you will ask yourself why and be afraid that your treatment will not bring recovery. You will ask yourself: Will I recover or die? Other people will still be afraid of him, they will still fear to get TB from him. They are afraid: Will he recover or not from his TB? If you get TB, it's very bad . . . it might happen that you will not recover." (patient quote; Bennstam et al., 2004)*

The significance of 'cure' - in addition to its inherent desirability as a "way to stay alive and healthy" - was further enacted as a 'gatekeeper' to patients' returning to normal functioning, and even the possibility that they might "flourish" (Reyes-Guillen *et al.*, 2008; Rundi, 2010; Zhang *et al.*, 2010).

> *"As a general rule, patients did not believe antituberculosis treatment could cure them, and that, consequently, they would not be able to continue living a normal life." (Reyes-Guillen* et al.*, 2008)*

Despite this, some still express fears that they will never sufficiently recover to achieve this (Rundi, 2010):

> *"Of course, it is difficult. Before I had this disease, I was only old. But whatever I want to do, I did it on my own. But now that I have this disease, although I am almost cured, according to the doctor, and my own feelings, I will definitely not recover completely as before. So, definitely it is difficult because before this illness, whatever work, I did it myself. But now, even near the house, even when I see all the plants withered away, I cannot do anything." (patient quote; Rundi, 2010)*

The importance of adherence is also enacted as a 'gatekeeper', first to cure, then (as described above) to patients' returning to normal functioning, and even the possibility that they might 'flourish' (Hu *et al.*, 2008; Queiroz *et al.*, 2012).

> *"I don't think it's necessary to be supervised by the doctor while taking drugs. Because of my poor economic situation, I really want to be cured as soon as possible, so I remember to take every dose. Even if I forget to take drugs before breakfast I will take it after that. No matter how many pills, I can take them." (patient quote; Hu et al., 2008)*

Poor reporting again led to moderate methodological concerns for these findings. There were severe concerns regarding the relevance of the findings because of the divergence of the phenomena of interest in the studies from those of the review and to the strong possibility that people with HIV were included in the study populations. There were mild concerns about coherence because other statements demonstrated a lack of trust in the capability of treatment to make them healthy again, particularly in those experiencing side effects from the treatment. However, it is perhaps not surprising that such conflicts exist given the difficulties experienced by many and the 'high stakes' of their situation. Although these findings were indirectly supported by other review findings (see related findings under 'Mortality and survival' and 'Treatment failure, success and cure'), there were mild to moderate concerns about the adequacy of the data due to the small amount of number of studies in which they were noted and due to the data not sufficiently reflecting the international and diverse patient group that a COS would apply to. Therefore, the overall confidence in these review findings was low.

The full review findings, including the constituent qualitative data and detailed CERQual assessments and scoring, can be found in Tables 10 and 11 below.

Table 10. Review findings and constituent qualitative data

Review finding	*Study*	*Study data*
Improvement in the signs and symptoms of disease'		
The physical and psychological impact of the symptoms of TB, and the relief felt when symptoms were alleviated, featured consistently in patients' narratives about their experiences of the disease.	Mafigiri, 2012	"'They say that it [TB] is very dangerous and they say that it is associated with HIV/AIDS. People say it has spread a lot in the community but more know it can be cured. Basing on the conditions that I was in, now my household members think it is important to treat TB because of the improvement and final healing that I have got. Even now my friends believe that it is important to treat TB because I have now cured and am feeling better.' Month-8 interview, Home-DOTS participant"
	Queiroz, 2012	"[TB] causes physical and mental pain" "positive aspects [of DOT]: improves signs and symptoms..."
	Reyes-Guillen, 2008	"Their main concerns were that treatment didn't get rid of the cough and it made them feel worse than the PTB itself –due to its adverse effects–; that is, a lack of improvement and feeling weaker."
	Zuñiga, 2014	"Weight loss was seen as a very negative side effect of TB. Several participants talked about being skinny and how horrible they looked. Five participants reported weight loss, some lost up to 40 pounds, and how much they had gained weight back since receiving treatment. One participant got tested for human immunodeficiency virus because his major symptom was weight loss, not a cough."
Antituberculosis treatment was viewed as a way to relieve the symptoms of the disease, which motivated patients to both adhere to and/or complete their treatment regimens.	Cramm, 2010	"'TB made me really sick. After I took the pills, I felt better again. When I take my pills for a few months, I am cured from TB. That is why I am going to finish my treatment.'"
	Naidoo, 2009	"Adherence to the program rested on a few factors, such as experiencing relief of the symptoms of the disease, the knowledge that another known person recovered from TB by taking the medication, and the hope that they

		would be cured by taking the treatment as prescribed. A 50-year-old female participant who readily took the treatment five months previously, at the onset of the infection, and continued to take the drugs because of the symptom relief she experienced, stated, 'I took my treatment frequently just like I'm doing right now. I didn't have any problems. Instead since I have been taking my treatment I feel a big relief even from the stiffness and the pain I always felt.'"
	Tadesse, 2013	"Weight gained during treatment and receiving improved laboratory results were reported to enhance compliance."
	Van den Boogaard, 2012	"A 28-year-old woman had attended several health care facilities before it was discovered that her backache was caused by spinal TB. She stated, 'For sure, the pain that I had, the way it has been relieved, I need to continue taking the medication.'"
Symptom relief seems to have additional significance as a surrogate - or even sign of hope - for recovery and survival. This link to recovery and survival appears to further bolster the motivation that symptom relief provides to adhere to and complete treatment. (See related findings under 'Mortality and survival' and 'Treatment failure, success and cure').	Bennstam, 2004	"'You go to the Health Center every day to check your weight. If it's not higher than last time, you will ask yourself why and be afraid that your treatment will not bring recovery. You will ask yourself: Will I recover or die? Other people will still be afraid of him, they will still fear to get TB from him. They are afraid: Will he recover or not from his TB? If you get TB, it's very bad . . . it might happen that you will not recover.'" [patient, HIV status unclear]
	Cramm, 2010	"'I don't like feeling sick. The pills from the clinic make me healthy, so I take them.'" "'TB made me really sick. After I took the pills, I felt better again. When I take my pills for a few months, I am cured from TB. That is why I am going to finish my treatment.'"
Mortality and survival		
Patients with TB reported fear of dying as a source of suffering.	Dias, 2013	"In this study, suffering was primarily caused by fear of dying, of transmitting the disease to others, and of being discriminated against, which is in accordance with the literature."

	Gerrish, 2012	"Whereas some were accepting of the diagnosis, for others self-stigma and fear of discrimination were real concerns: 'I was very shocked. People are scared of TB because they think they'll die...' [patient]"
	Zhang, 2010	"In their minds, PTB is a very serious disease that would badly harm them. Some of them considered PTB as a disease that could not be cured, and some even feared that they would die from PTB." "'At the news that I was diagnosed with PTB, I was badly fearful. When I was a child, I often heard that if one suffered from it...he would die.' (Male, 20 years old, continuation phase, outpatient)"
Tuberculosis was viewed as a "deadly disease" and antituberculosis treatment as a "way to stay alive and healthy", which motivated patients to both adhere to and/or complete their treatment regimens. The possibility that that they might die from their disease caused patients to enact positive health behaviours.	Van den Boogaard, 2012	"'I remember my own brother, who was working in the bush. He got tuberculosis and he stayed in the hospital for almost two years, and thereafter he was discharged. But he was not following the instructions [of the doctor]. He was drinking and sometimes smoking, so the tuberculosis, again he got it. So when he was returned to the hospital, it was in vain. He died. So I decided to take it strongly, because I was remembering my brother and I did not want the same to happen to me.'"
	Dias, 2013	"In the context of this study, respondents regarded treatment as a way to stay alive and healthy, which may have contributed to their adherence to treatment. 'Because when we'd hear about tuberculosis, it was said to be a deadly disease.' 'I felt that I had to do my very best not to skip a single day of treatment.'"
Treatment failure, success and cure		
Many patients doubted that treatment will cure their disease completely.	Acha, 2007	"Due to years of illness, many patients had grave doubts as to whether or not treatment would be effective. Previous treatment failures had taught them to be skeptical, and this seed of doubt often persisted throughout the 2-year treatment."
	Khan, 2012	"Complete curability of the disease also was doubted by participants, reflecting a mix of distrust in biomedicine, the incurability of the stigma, and

		the living realities that often constrain the completion of treatment regimen. As summed by a woman, 'It is impossible for a TB patient to get completely cured. … Once a person gets infected, the disease will keep resurfacing.' This reflected the lasting mark that TB left on people who contracted it irrespective of whether they were cured or not."
	Mafigiri, 2012	"Participants reacted with fear, shock and anger because they regarded TB as a deadly disease with no cure. 'In December [2004] when I first had symptoms, it was flu then later I started coughing so after all the treatment with no improvement, I opted for better treatment here in Mulago … I got so scared because I have always heard that it doesn't cure.' Baseline interview, Clinic-DOTS participant"
	Reyes-Guillen, 2008	"As a general rule, patients did not believe antituberculosis treatment could cure them."
	Zhang, 2010	"'I had a fever. I told myself that I just caught a cold and everything would be fine. However, it could not be cured for a long time. I began to feel upset--worse and worse.' (Male, 21 years old, intensive phase, inpatient)" "Some of them considered PTB as a disease that could not be cured, and some even feared that they would die from PTB."
	Gerrish, 2013	"Although patients believed that they could make a good recovery, several were concerned that they could not be cured completely: a view linked to a belief that TB was hereditary. 'I have taken the tablets, they tell me I am cured, but the TB, I think it may come back. It's in my family.' (Patient 4) This caused anxiety as they believed distressing symptoms might return and carry implications for social relationships."
	Van den Boogaard, 2012	"Knowledge and beliefs about TB treatment. This theme consisted of three interrelated subthemes: (a) general beliefs and perceptions of TB disease, (b) the belief that TB is curable, and (c) the belief that the doctor's instructions need to be followed to be cured. The participants' confidence in biomedical health care—i.e., biomedicine as opposed to traditional medicine such as

		witchcraft and herbal medicine, which are widely available in Tanzania — recurred within all subthemes ... All participants believed that TB is curable … Participants reported on several sources of information that helped them to believe that TB is curable. Some participants had read about TB treatment on health education posters in health care facilities. Most participants believed that TB is curable because they had heard from others who were cured after using the medication as prescribed. In addition, the participants had experienced a substantial improvement in their health after they started TB treatment, and this strengthened their belief that TB is curable."
Antituberculosis treatment was viewed as a "way to stay alive and healthy", which motivated patients to both adhere to and/or complete their treatment regimens.	Cramm, 2010	'"TB made me really sick. After I took the pills, I felt better again. When I take my pills for a few months, I am cured from TB. That is why I am going to finish my treatment."'
	Cramm, 2010	'I take my treatment because I really want to get healthy again' – compliers +2, noncompliers 0; quantitative (scale -3 to +3) - exclude?
	Hu, 2008	"Many patients reported it was unnecessary to be directly observed by a doctor. They felt they were able to remember to take the medicine by themselves; some said they were motivated to take their drugs because they wanted to be cured and recover." Patient quotes: "'Q: Even in the hospital, no doctor supervised you? A: The patient should have self-awareness to take the drug; otherwise he cannot be cured.' (Male, retreated patient, JLP county)" "'It's not necessary. I have self-consciousness; I don't want to waste their time, they are so busy. I should be responsible to myself, because I want to recover.' (Female, new patient, RC county)" "'I don't think it's necessary to be supervised by the doctor while taking drugs. Because of my poor economic situation, I really want to be cured as soon as possible, so I remember to take every dose. Even if I forget to take drugs before breakfast I will take it after that. No matter how many pills, I can take them.' (Male, retreated patient, RC count)"

		"'I don't think it's necessary. I want to be cured as early as possible, so I always take drugs on time.' (Female, new patient, LB county)" "'I want to be cured, how can I forget to take drugs? No, I won't.' (Male, new patient, RC county)"
	Mafigiri, 2012	"'They say that it [TB] is very dangerous and they say that it is associated with HIV/AIDS. People say it has spread a lot in the community but more know it can be cured. Basing on the conditions that I was in, now my household members think it is important to treat TB because of the improvement and final healing that I have got. Even now my friends believe that it is important to treat TB because I have now cured and am feeling better.' Month-8 interview, Home-DOTS participant"
	Naidoo, 2009	"Adherence to the program rested on a few factors, such as experiencing relief of the symptoms of the disease, the knowledge that another known person recovered from TB by taking the medication, and the hope that they would be cured by taking the treatment as prescribed." "A 20-year-old participant who had been diagnosed with TB five months previously related how the fact that his family member was cured from the disease made him hopeful that he would be cured if he adhered to the treatment program: 'You see my older brother once had TB and he used to cough a lot when it started. But then he got better again because he was eating treatment. So like when I was told that I have TB it wasn't a big deal because I knew that it can be cured.'"

	Van den Boogaard, 2012	"The main themes underlying this intention to adhere were knowledge and beliefs about TB treatment [This theme consisted of three interrelated subthemes: (a) general beliefs and perceptions of TB disease ["... All participants believed that TB is curable"], (b) the belief that TB is curable, and (c) the belief that the doctor's instructions need to be followed to be cured"] and the motivation to be cured." "To the question why the participants were managing so well at taking their medication every day, many participants responded that they wanted to be cured."
Adverse effects of treatment		
The adverse effects of regimens featured consistently in patients' narratives about the burden of treatment.	Acha, 2007	"Frequent nausea and vomiting were also common, and patients commiserated over this with one another, and shared concrete strategies to minimize this reaction. For example, one patient told the group: 'I used to throw up every day. As soon as I would hear the health worker's knock on the door, I would begin to feel nauseated. I would take the medicines, and then throw up immediately. The worst was that then I would have to take them again, and again, until I could get them to stay down. I found that when I would take them on an empty stomach, it was worse. Now I take them with fruit, or yoghurt, and it helps. It takes the taste out of my mouth and I'm able to resist (vomiting). Now I rarely throw up. I'm able to keep them down, but always on a full stomach.'" "Another very difficult side effect was the darkening of the pigmentation in the skin that was caused by one medication, clofazamine. Negative attitudes towards darker skin colour in Peruvian culture made this particular side-effect difficult to manage, especially when compounded by the marginalization these patients already experienced due to their disease. Patients reported constantly needing to deflect comments and questions about their skin colour to friends and neighbours, while attempting to keep their disease a secret, often being reduced to lies. As one patient expressed: 'I've had to learn to be a liar. When people ask why my skin is so dark, I say

		I've gone to the beach, or into the mountains. I mean, what can I do? I have to come up with whatever lie I can besides the truth, anything but the truth, because if they found out the truth, they would discriminate against me. Who wants to be marginalized? One has to lie.' The support groups helped patients to accept their pigmented skin, emphasizing that their health was most important, and that they would have to tolerate this side effect in order to be cured of their disease. As one patient summarized, 'I just think of it as ''either I'm black or I'm dead'' and I want to live.'"
	Franck, 2014	"'They make me feel dizzy. [...] And they made me feel pain in my stomach.' (Child, 11b)" "The majority of respondents cited the large number of pills and their adverse effects to be the most challenging components of treatment."
	Paz, 2009	"'When I take the medication I feel sick, get weak and feel just like lying. At the beginning it was worse because I got sickness, stomach ache, vomiting, but then it all passed. Now, I only have back pain and tiredness, but they told me it is like this, I have to be patient 'cause it'll get better. I almost can't close my hands because of my joint pain, sometimes I feel like stopping the medication, but I think about my family, myself and keep going, but I'm getting better.'(Interview 15 – Infected)."
	van Elsland, 2012	"Although the procedure to administer medication was easy, giving medication was quite difficult for most caretakers: 'We had to struggle …fight with him.' Vomiting often complicated administration of medication while bad taste and odor of medication were reported to cause nausea. Other side effects mentioned were weight gain, skin rashes and behavioral changes (motor restlessness and aggression)."
	Reyes-Guillen, 2008	"Their main concerns were that treatment didn't get rid of the cough and it made them feel worse than the PTB itself –due to its adverse effects–; that is, a lack of improvement and feeling weaker."

Patients reported that the adverse effects experienced "could be as severe or more severe" than the disease itself.		"'There's no way I'm going to keep taking this medicine if it makes me feel even worse.'"
	Zuñiga, 2014	"The symptoms changed relatively quickly for the participants after treatment began. The side effects of the medication could be as severe or more severe than the symptoms of TB for many participants. In some cases the side effect of nausea was so difficult for the participant that the doctor offered intravenous medication in inpatient treatment, although none of the participants took this option. 'I felt that that wasn't a very good treatment for me because I felt that it started affecting parts of my body. I felt nauseous … I started feeling the fatigue. My finger started to feel really stiff. The bone ache, the tiredness … I blame the pill treatment. It was all happening because of that because I was fine when I was released [from the hospital]. After that treatment I started feeling all those symptoms.' (Participant 2, translated from Spanish)"
The adverse effects of the antituberculosis drugs was a barrier both to patients adhering to their treatment regimens and to the completion of the full treatment period. The physical, psychological and social burden of the adverse effects of treatment (see above) made patients "want to give up".	Franck, 2014	"Adverse effects coupled with exceptionally long treatment duration rendered adherence difficult, particularly among HIV-positive children concurrently taking anti- retroviral therapy (ART) and treatment for MDR-TB."
	Paz, 2009	"'When I take the medication I feel sick, get weak and feel just like lying. At the beginning it was worse because I got sickness, stomach ache, vomiting, but then it all passed. Now, I only have back pain and tiredness, but they told me it is like this, I have to be patient 'cause it'll get better. I almost can't close my hands because of my joint pain, sometimes I feel like stopping the medication, but I think about my family, myself and keep going, but I'm getting better.' (Interview 15 – Infected). 'At the beginning you want to give up because the medication side effects are too much, it made me feel very sick, had to go hospital, my pressure would go up, I felt weak, it was really bad. At the beginning of the treatment I'd only lie in bed, had no energy to do anything, now I feel I have more disposition, even want to go back to work, I feel really well… I'm feeling really well, just my blood pressure is altered, I get swollen and my bones ache, but I'll get to

		the end of the treatment…' (Interview 7 - Infected)" "Another marked aspect in the patients' life is the difficulty to correctly follow the treatment because of the toxicity chemotherapy can cause."
	Tadesse, 2013	"Actual events of adverse drug reactions and fear of possible adverse drug reactions reduced treatment compliance."
	Xu, 2009	"In-depth interviews among both TB patients and local doctors indicate that adverse drug reaction is a reason for treatment non-adherence. Fear of the risks of adverse drug reactions leads some TB patients to interrupt treatment. Local health workers often cannot detect this discontinuation of treatment due to the lack of an active adverse drug reaction surveillance system under the current DOTS program. 'The majority of TB patients in my village have good adherence to treatment. However, some patients are reluctant to cooperate with us. The main reasons are the adverse reactions and long course of treatment. For example, one patient didn't visit my clinic to take drugs as regularly. So I called him immediately. He told me that he didn't want to continue as he felt much more uncomfortable after taking drugs.'" [NB. quote from Doctor; no patient quote]
	Zuñiga, 2014	"They also balanced the benefits of taking their medication with the negative side effects of the medication. The need to finish treatment had to be balanced against the nausea, fatigue, and weakness. Several of the participants talked of other patients leaving the DOTS program. They had heard about patients leaving for Mexico because they did not want to finish treatment."
There was concern amongst some patients that the physical impact of the adverse effects of treatment regimens may stretch far beyond the end of treatment or cure of the disease, and may have long-term consequences in terms of their ability to function and, beyond that, to flourish.	Zhang, 2010	"Some patients were worried that the side effects of anti- TB drugs would exist for long terms, especially the outcome of infertility and impaired function of liver and kidney."
	Zuñiga, 2014	"'It is said that taking anti-TB drugs might lower fertility, I am rather worried about it.' (Male, 20 years old, continuation phase, outpatient)"

In addition to the physical experience, patients reported psychosocial impacts arising from the adverse effects of treatment regimens.	Paz-Soldan, 2013	"Others mentioned that the medications made them feel so queasy and tired that they no longer felt like going out in public. A number of TB positive men, for example, mentioned that they used to play soccer and then drink beer with their friends, but during treatment had no energy for soccer and were not allowed to drink alcohol, so as a result they saw their friends significantly less."
	Sagbakken, 2008	"Patients attributed side effects, such as gastritis, nausea, and vomiting, to taking strong medicines on an empty stomach. These side effects had a large psychological impact: Since most patients considered access to food, and particularly food with a high content of protein, as extremely important to healing, symptoms as gastritis served as a continuous reminder of their poverty and what they considered to be poor healing conditions."
	Van den Boogaard, 2012	"Adverse effects of treatment (such as feeling hungry) aggravated the perceived socioeconomic difficulties that participants had to cope with."
For those on the more intensive regimens necessitated by drug-resistant disease, the psychological impact of adverse effects even extended to suicidal ideation.	Acha, 2007	"'All of us go through that (suicidal ideation); that's normal. The beginning of treatment is so hard, but it gets easier. I thought about killing myself many times. The side effects were so bad; I was so depressed. Treatment seemed like an eternity. But little by little, things got better.'"
Impact on functioning		
Patients reported a range of limitations – social, physical, developmental, educational, economic – to their ability to function. These was imposed both by the treatment of their TB and by the disease itself, and affected their wellbeing and their ability to 'flourish'.	Acha, 2007	"Another common frustration among patients was related to the restrictions imposed by their disease and/or treatment. Due to MDR-TB, many patients experienced physical ailments related to their disease, such as shortness of breath, fatigue, or wasting, in addition to various physical side effects caused by the medications, such as headaches, gastritis, or peripheral neuropathy. These physical ailments prevented some patients from fulfilling important occupational or social roles."
	Gerrish, 2013	"The longer term consequences of the disease were keenly felt. Participants who had completed treatment recounted how it took some considerable time

		before they felt better: 'I was very ill. It is everything to get back to normal life, to feel fit and strong. It took three years to get back to normal, to find a job.' (Patient 11)"
There was concern that the treatment of TB or the disease itself may have an impact on the education and development of children and young people affected	Acha, 2007	"Often younger patients had to overcome the frustration of thwarted plans to study and develop personally and/or professionally and put their lives on hold while they struggled to overcome the disease."
	Franck, 2014	"A few caregivers used the term “slow” to describe a change in the child’s academic abilities, or even more generally, their intellectual capabilities. '[A]fter that treatment she forgets everything. […] I’m worried because when she did grade one before she went to hospital, she was so clever, very, very brilliant.' (Caregiver, 9a) 'She is a bit slow, she is not doing well at school anymore so next year she is going to another school. I think [her old friends] have noticed she is different, because she does not play with the big children, she plays with the small children.' (Caregiver, 11c) 'The school was calling me, she was very slow at her work.' (Caregiver, 11d) While no cause was identified for this trend, decreased academic performance and behavioural changes may be attributed to a range of factors, including adverse effects from medications, and the difficulty of returning to the pace of a normal academic curriculum."
Patients reported that the treatment of TB and the affects of disease itself affected their ability to work. In addition to the loss of wages that this is associated with, as well as the subsequent financial hardship, patients described "feelings of ‘uselessness’ and being ‘a burden’ on their already struggling families."	Acha, 2007	"Former wage earners strained to overcome feelings of ‘uselessness’ and being ‘a burden’ on their already struggling families as a result of their inability to work."
	Gerrish, 2013	"The social impact of their illness over a prolonged period of time was notable. Patients found it hard to maintain social networks. Two patients were unable to continue in employment and loss of income as well as status was distressing."
	Reyes-Guillen, 2008	"Their worries about PTB were greater when physically unable to work (‘before I could work my land, now I can’t…’)."

	Cramm, 2010	"Contrary to the 'most important' factors, there was much less consensus among compliers regarding the 'least important' factors. Compliers indicate that the possible loss of wages, the social stigma, home visits by the community health worker, the chance of dying of TB, and the burden of taking medication were least important for them. They do not experience or pay much attention to these barriers and supports, apparently because treatment is going well."
Patients reported social impacts from the treatment and experience of disease. Some experienced feelings of social isolation (an isolation perhaps compounded by discrimination arising from the disease itself) because they lacked energy to join in with social activities, such as playing sports or drinking, or simply no longer felt like going out in public, making it difficult to maintain relationships.	Acha, 2007	"Many patients were also frustrated by social limitations; some lacked energy to adequately care for their children, and others experienced difficult strains on their intimate relationships."
	Gerrish, 2013	"The social impact of their illness over a prolonged period of time was notable. Patients found it hard to maintain social networks. Two patients were unable to continue in employment and loss of income as well as status was distressing ... [Some] patients reported that their initial experience of social isolation reduced once they made known that they were responding well to treatment."
	Paz-Soldan, 2013	"Others mentioned that the medications made them feel so queasy and tired that they no longer felt like going out in public. A number of TB positive men, for example, mentioned that they used to play soccer and then drink beer with their friends, but during treatment had no energy for soccer and were not allowed to drink alcohol, so as a result they saw their friends significantly less."
The significance of 'cure' - in addition to its inherent desirability as a "way to stay alive and healthy" - was further enacted as a 'gatekeeper' to patients' returning to normal functioning, and even the possibility that they might "flourish".	Reyes-Guillen, 2008	"As a general rule, patients did not believe anti- tuberculosis treatment could cure them, and that, consequently, they would not be able to continue living a normal life, especially with regard to the treatment's adverse effects ('There's no way I'm going to keep taking this medicine if it makes me feel even worse')."
	Zhang, 2010	"'Everything will be difficult for me, if I could not be cured. Maybe I will not be employed…' (Male, 22 years old, intensive phase, inpatient)"

	Rundi, 2010	"Many [patients], particularly men, felt that, as a result of TB, they often felt weak and never fully recover to their pre-illness physical state. Patients who were farmers find it difficult to continue farming due to residual weakness. 'Of course, it is difficult. Before I had this disease, I was only old. But whatever I want to do, I did it on my own. But now that I have this disease, although I am almost cured, according to the doctor, and my own feelings, I will definitely not recover completely as before. So, definitely it is difficult because before this illness, whatever work, I did it myself. But now, even near the house, even when I see all the plants withered away, I cannot do anything.' (A 60-year old farmer)"
The importance of adherence is also enacted as a 'gatekeeper', first to cure, then (as described above) to patients' returning to normal functioning, and even the possibility that they might "flourish".	Queiroz, 2012	"[Treatment adherence] is a result of one's desire to improve physical condition and resume activities and life plans set aside because of the disease and also of the encouragement provided by family and the providers at the PCU."
	Hu, 2008	"'I don't think it's necessary to be supervised by the doctor while taking drugs. Because of my poor economic situation, I really want to be cured as soon as possible, so I remember to take every dose. Even if I forget to take drugs before breakfast I will take it after that. No matter how many pills, I can take them.' (Male, retreated patient, RC count)"

Table 11. CERQual profiles

Review finding	*Studies contributing to the review finding*	*Assessment of methodological limitations*	*Assessment of relevance*	*Assessment of coherence*	*Assessment of adequacy*	*Overall CERQual assessment of confidence*
Improvement in the signs and symptoms of disease						

The physical and psychological impact of the symptoms of TB, and the relief felt when symptoms were alleviated, featured consistently in patients' narratives about their experiences of the disease.	Mafigiri, 2012 Queiroz, 2012 Reyes-Guillen, 2008 Zuñiga, 2014	Moderate methodological limitations (-2): Unclear if 3 studies took the relationship between researcher and participants into consideration The approach to sampling was unclear in 3 studies The approach to data analysis was unclear in 2 studies No study reported treatment regimen used Patient quotes for this finding was provided by/ identified in only 1 study	Severe concerns about relevance (-3): No study was designed to directly examine the prioritisation of treatment outcomes Some concern over relevance of population: HIV status not described in any study (national data for 1 study suggested high prevalence); 1 study reported other comorbidities that may affect management and its experience (over half had diabetes; 1had kidney failure and was on dialysis three times a week; 1 had cirrhosis of the liver)	No concerns about coherence	Moderate concerns about adequacy (-2): Although data felt rich in the varied descriptions of the phenomena, it came from just 4 studies, conducted in 4 countries (3 Central/South America, 1 Africa); the disease was primarily respiratory, and patients were adults only generally from poorer, urban settings.	Low confidence (score: 5/12)

Antituberculosis treatment was viewed as a way to relieve the symptoms of the disease, which motivated patients to both adhere to and/or complete their treatment regimens.	Cramm, 2010 Naidoo, 2009 Tadesse, 2013 Van den Boogaard, 2012	Moderate methodological limitations (-2): Unclear if 2 studies took the relationship between researcher and participants into consideration The approach to sampling was unclear in 1 study Limited provision of population characteristics (most notably site of disease) in all studies No study reported treatment regimen used Patient quotes not provided by/identified in 1 study for this finding	Severe concerns about relevance (-3): No study was designed to directly examine the prioritisation of treatment outcomes Some concern over relevance of population: HIV status not described in 2 studies (national data suggested moderate and high prevalences); in 1 study 4 of the 11 participants had HIV, though only 2 were on ART, and in another study 7 of 15 were HIV-positive (not on ART) and 2 were unknown – extraction for these was avoided	Mild concerns about coherence (-1): Although patients reported that they viewed antituberculosis treatment as a way to relieve the symptoms of the disease and that this led them to adhere to treatment, other statements demonstrated a lack of trust in the power of treatment to make them healthy again, particularly in those experiencing side effects from the treatment; however, it is perhaps not surprising that such conflicts exist given the difficulties experienced by many	Moderate concerns about adequacy (-2): Although data felt rich in the varied descriptions of the phenomena, and was indirectly supported by other findings, it came from just 4 studies, conducted solely in Sub-Saharan Africa; there were few, if any, children included, and patients were all from poorer settings.	Very low confidence (score: 4/12)

Symptom relief seems to have additional significance as a surrogate - or even sign of hope - for recovery and survival. This link to recovery and survival appears to further bolster the motivation that symptom relief provides to adhere to and complete treatment. *(See related findings under 'Mortality and survival' and 'Treatment failure, success and cure').*	Bennstam, 2004 Cramm, 2010	Moderate methodological limitations (-2): Unclear if the relationship between researcher and participants was taken into consideration in either study The approach to sampling was unclear in 1 study Limited provision of population characteristics (most notably site of disease) in both studies No study reported treatment regimen used Patient quotes available Evidence may not be from patients in 1 study	Severe concerns about relevance (-3): No study was designed to directly examine the prioritisation of treatment outcomes Some concern over relevance of population: HIV status not described in any study (national data for 1 study suggested high prevalence)	Mild concerns about coherence (-1): Although patients reported that they viewed antituberculosis treatment as a way to relieve the symptoms, linking it to cure and survival, which in turn provided greater motivation to adhere to treatment, other statements demonstrated a lack of trust in the power of treatment to make them healthy again or to keep them alive; however, it is perhaps not surprising that such conflicts exist given the difficulties experienced by many and the 'high stakes' of their situation	Severe concerns about adequacy (-3): Data felt thin in its descriptions of the phenomena (although it was indirectly supported by other findings), and it it came from just 2 studies conducted solely in Sub-Saharan Africa; there were few, if any, children included, and patients were all from poorer settings	Very low confidence (score: 3/12)
Mortality and survival						

Patients with TB reported fear of dying as a source of suffering.	Dias, 2013 Gerrish, 2012 Zhang, 2010	Moderate methodological limitation (-2): Unclear if the relationship between researcher and participants was taken into consideration in 1 study Limited provision of population characteristics (most notably site of disease) in 1 study No study reported treatment regimen used Patient quotes not provided by/identified in 2 studies for this finding	Moderate concerns about relevance (-2): No study was designed to directly examine the prioritisation of treatment outcomes Some concern over relevance of population: HIV status not described in 2 studies (national data do not suggest high prevalence, however); third study HIV-negative	No concerns about coherence	Mild concerns about adequacy (-1): Although data felt fairly rich in the descriptions of the phenomena, it came from just 3 studies; there were few, if any, children included	Low confidence (score: 7/12)

Tuberculosis was viewed as a "deadly disease" and antituberculosis treatment as a "way to stay alive and healthy", which motivated patients to both adhere to and/or complete their treatment regimens. The possibility that that they might die from their disease caused patients to enact positive health behaviours. *(See related findings under 'Improvement in the signs and symptoms of disease' and 'Treatment failure, success and cure').*	Cramm, 2010 Dias, 2013 Van den Boogaard, 2012	Moderate methodological limitations (-2): Unclear if 2 studies took the relationship between researcher and participants into consideration The approach to sampling was unclear in 1 study Limited provision of population characteristics (most notably site of disease) in 2 studies No study reported treatment regimen used Patient quotes not provided by/identified in 1 studies for this finding	Severe concerns about relevance (-3): No study was designed to directly examine the prioritisation of treatment outcomes Some concern over relevance of population: HIV status not described in 1 study (national data suggest high prevalence); 1 study HIV-negative; in third study 4 of the 11 participants had HIV, though only 2 were on ART (avoided extraction)	Mild concerns about coherence (-1): Although patients reported that they viewed antituberculosis treatment as a way to stay alive, which in turn provided greater motivation to adhere to treatment, other statements demonstrated a lack of trust in the power of treatment to make them healthy again or to keep them alive; however, it is perhaps not surprising that such conflicts exist given the difficulties experienced by many and the 'high stakes' of their situation	Mild concerns about adequacy (-1): Although data felt rich in the varied descriptions of the phenomena, and was indirectly supported by other findings, it came from just 3 studies, conducted in 4 countries (1 South America, 2 Africa); there were few, if any, children included, and patients were all from poorer settings	Low confidence (score: 5/12)
Treatment failure, success and cure						

Many patients doubted that treatment will cure their disease completely.	Acha, 2007 Khan, 2012 Mafigiri, 2012 Reyes-Guillen, 2008 Zhang, 2010 Gerrish, 2013 Van den Boogaard, 2012	Moderate methodological limitations (-2): Unclear if 3 studies took the relationship between researcher and participants into consideration The approach to data analysis was unclear in 2 studies and the details limited in 1 further study The approach to sampling was unclear in 2 studies Limited provision of population characteristics (most notably site of disease) in 5 studies No study reported treatment regimen used 1 study did not provide the number of patients included Patient quotes not provided by/identified in 3 studies for this finding Evidence may not be from patients (family members) in 1 study	Severe concerns about relevance (-3): No study was designed to directly examine the prioritisation of treatment outcomes Some concern over relevance of population: HIV status not described in 5 studies (national data suggest high prevalence in 1); 1 study HIV-negative; in another study 4 of the 11 participants had HIV, though only 2 were on ART (avoided extraction)	Mild concerns about coherence (-1): Although patients reported that they doubted that treatment will cure their disease completely, statements were also identified that showed belief that antituberculosis treatment was as a way to make them healthy again and to keep them alive; however, it is perhaps not surprising that such conflicts exist given the difficulties experienced by many and the 'high stakes' of their situation	No concerns about adequacy	Low confidence (score: 6/12)

Antituberculosis treatment was viewed as a "way to stay alive and healthy", which motivated patients to both adhere to and/or complete their treatment regimens. *(See related findings under 'Improvement in the signs and symptoms of disease' and 'Mortality and survival).*	Cramm, 2010 Hu, 2008 Mafigiri, 2012 Naidoo, 2009 Van den Boogaard, 2012	Moderate methodological limitations (-2): Unclear if 3 studies took the relationship between researcher and participants into consideration The approach to data analysis was unclear in 1 study The approach to sampling was unclear in 1 study Limited provision of population characteristics (most notably site of disease) in 5 studies No study reported treatment regimen used Patient quotes not provided by/identified in 1 study for this finding	Severe concerns about relevance (-3): No study was designed to directly examine the prioritisation of treatment outcomes Some concern over relevance of population: HIV status not described in 4 studies (national data suggest high prevalence in 2); in 1 study 4 of the 11 participants had HIV, though only 2 were on ART, and in another study 7 of 15 were HIV-positive (not on ART) and 2 were unknown – extraction for these was avoided	Mild concerns about coherence (-1): Although patients reported that they viewed antituberculosis treatment as a way to recover, which in turn provided greater motivation to adhere to treatment, other statements demonstrated a lack of trust in the power of treatment to make them healthy again or to keep them alive; however, it is perhaps not surprising that such conflicts exist given the difficulties experienced by many and the 'high stakes' of their situation	Mild concerns about adequacy (-1): Although data felt rich in the varied descriptions of the phenomena, and was indirectly supported by other findings, it came from studies conducted in 4 countries primarily in Sub-Saharan Africa, with just 1 conducted outside of the region (in China); there were few, if any, children included, and patients were all from poorer settings	Low confidence (score: 5/12)
Adverse effects of treatment						

The adverse effects of regimens featured consistently in patients' narratives about the burden of treatment.	Acha, 2007 Franck, 2014 Paz, 2009 van Elsland, 2012	Moderate methodological limitations (-2): Unclear if 4 studies took the relationship between researcher and participants into consideration The approach to data analysis was unclear in 2 studies The approach to sampling was unclear in 2 studies Limited provision of population characteristics (most notably site of disease) in 4 studies No study reported treatment regimen used 1 study did not provide the number of patients included Patient quotes not provided by/identified in 1 study for this finding Evidence may not be from patients (family members) in 3 studies	Moderate concerns about relevance (-2): No study was designed to directly examine the prioritisation of treatment outcomes No study was designed to directly examine the prioritisation of treatment outcomes Some concern over relevance of population: HIV status not described in 3 studies (national data suggest high prevalence in 1); 2 studies HIV-negative	No concerns about coherence	Mild concerns about adequacy (-1): Although data felt rich in the varied descriptions of the phenomena, it came from just 4 studies, conducted primarily in urban settings in only 4 countries (2 South America, 2 Sub-Saharan Africa)	Low confidence (score: 7/12)

Patients reported that the adverse effects experienced "could be as severe or more severe" than the disease itself.	Reyes-Guillen, 2008 Zuñiga, 2014	Moderate methodological limitations (-2): Unclear if the relationship between researcher and participants was taken into consideration in 1 study The approach to sampling was unclear in both studies Limited provision of population characteristics (most notably site of disease) in 1 study No study reported treatment regimen used Patient quotes provided by/identified	Severe concerns about relevance (-3): No study was designed to directly examine the prioritisation of treatment outcomes Some concern over relevance of population: HIV status not described in any study (national data did not suggest high prevalence); 1 study reported other comorbidities that may affect management and its experience (over half had diabetes; 1had kidney failure and was on dialysis three times a week; 1 had cirrhosis of the liver)	No concerns about coherence	Moderate concerns about adequacy (-2): Data was thin and came from just 2 studies, both conducted in or around Mexico	Low confidence (score: 5/12)

The adverse effects of the antituberculosis drugs was a barrier both to patients adhering to their treatment regimens and to the completion of the full treatment period. The physical, psychological and social burden of the adverse effects of treatment (see above) made patients "want to give up".	Franck, 2014 Paz, 2009 Tadesse, 2013 Xu, 2009 Zuñiga, 2014	Moderate methodological limitations (-2): Unclear if the relationship between researcher and participants was taken into consideration in 4 of the studies The approach to sampling was unclear in 2 studies Limited provision of population characteristics (most notably site of disease) in all studies No study reported treatment regimen used Patient quotes not provided by/identified in 3 studies for this finding Evidence may not be from patients (family members) in 1 study	Severe concerns about relevance (-3): No study was designed to directly examine the prioritisation of treatment outcomes Some concern over relevance of population: HIV status not described in any study (national data did not suggest high prevalence); 1 study reported other comorbidities that may affect management and its experience (over half had diabetes; 1had kidney failure and was on dialysis three times a week; 1 had cirrhosis of the liver) Additionally, some evidence came from people other than patients (doctor) in 1 study	No concerns about coherence	No concerns about adequacy	Low confidence (score: 7/12)

There was concern amongst some patients that the physical impact of the adverse effects of treatment regimens may stretch far beyond the end of treatment or cure of the disease, and may have long-term consequences in terms of their ability to function and, beyond that, to flourish. *(See related findings under 'Impact on functioning').*	Zhang, 2010 Zuñiga, 2014	Moderate methodological limitations (-2): The approach to sampling was unclear in 1 study Limited provision of population characteristics (most notably site of disease) in 1 study No study reported treatment regimen used Patient quotes not provided by/identified in 1 study for this finding	Severe concerns about relevance (-3): No study was designed to directly examine the prioritisation of treatment outcomes Some concern over relevance of population: HIV status not described in either study (national data did not suggest high prevalence); 1 study reported other comorbidities that may affect management and its experience (over half had diabetes; 1had kidney failure and was on dialysis three times a week; 1 had cirrhosis of the liver)	No concerns about coherence	Moderate concerns about adequacy (-2): Data seemed fairly thin, although it was indirectly supported by other findings; it came from just 2 studies conducted in poorer settings, sampling adults only	Low confidence (score: 5/12)

In addition to the physical experience, patients reported psychosocial impacts arising from the adverse effects of treatment regimens.	Paz-Soldan, 2013 Sagbakken, 2008 Van den Boogaard, 2012 Acha, 2007	Moderate methodological limitations (-2): Unclear if the relationship between researcher and participants was taken into consideration in 1 study Limited provision of population characteristics (most notably site of disease) in all studies No study reported treatment regimen used Patient quotes not provided by/identified in any study for this finding	Severe concerns about relevance (-3): No study was designed to directly examine the prioritisation of treatment outcomes Some concern over relevance of population: HIV status not described in 1 study (national data suggests high prevalence in 1); in 1 study 4 of the 11 participants had HIV, though only 2 were on ART, and in another study 11 of 43 were HIV-positive – extraction for these was avoided	No concerns about coherence	Mild concerns about adequacy (-1): Although data felt fairly rich in the varied descriptions of the phenomena, it came from just 4 studies, conducted primarily in urban settings in only 3 countries (2 studies in South America, 2 Sub-Saharan Africa)	Low confidence (score: 6/12)

For those on the more intensive regimens necessitated by drug-resistant disease, the psychological impact of adverse effects even extended to suicidal ideation.	Acha, 2007	Moderate methodological limitations (-2): Unclear if the relationship between researcher and participants was taken into consideration Approach to analysis unclear Approach to sampling unclear Limited provision of population characteristics (most notably site of disease) Study did not report treatment regimen used Study did not provide the number of patients included Quotes provided by/identified, though may not be from patients (family members)	Moderate concerns about relevance (-2): No study was designed to directly examine the prioritisation of treatment outcomes	No concerns about coherence	Severe concerns about adequacy (-3): Finding based on just 1 study	Very low confidence (score: 5/12)
Impact on functioning						

Patients reported a range of limitations – social, physical, developmental, educational, economic – to their ability to function. These was imposed both by the treatment of their TB and by the disease itself, and affected their wellbeing and their ability to 'flourish'.	Acha, 2007 Cramm, 2010 Franck, 2014 Gerrish, 2013 Hu, 2008 Paz-Soldan, 2013 Queiroz, 2012 Reyes-Guillen, 2008 Rundi, 2010 Zhang, 2010	Moderate methodological limitations (-2): Unclear if 7 studies took the relationship between researcher and participants into consideration The approach to data analysis was unclear in 2 studies The approach to sampling was unclear in 4 studies Limited provision of population characteristics (most notably site of disease) in 8 studies No study reported treatment regimen used 1 study did not provide the number of patients included Patient quotes not provided by/identified in 4 studies for this finding Evidence may not be from patients (family members) in 2 studies	Moderate concerns about relevance (-2): No study was designed to directly examine the prioritisation of treatment outcomes Some concern over relevance of population: HIV status not described in 9 studies (national data suggest high prevalence in 2); 1 study HIV-negative; in another study 11 of 43 were HIV-positive (avoided extraction)	No concerns about coherence	No concerns about adequacy	Moderate confidence (score: 8/12)

There was concern that the treatment of TB or the disease itself may have an impact on the education and development of children and young people affected.	Acha, 2007 Franck, 2014	Moderate methodological limitations (-2): Unclear if the relationship between researcher and participants was taken into consideration in either study Approach to analysis unclear in 1 study Approach to sampling unclear in 1 study Limited provision of population characteristics (most notably site of disease) in either study No study reported treatment regimen used 1 study did not provide the number of patients included Patient quotes not provided by/identified in 1 study for this finding Evidence may not be from patients (family members)	Moderate concerns about relevance (-2): No study was designed to directly examine the prioritisation of treatment outcomes Some concern over relevance of population: HIV status not described in 1 study (national data suggested high prevalence); 1 study HIV-negative	No concerns about coherence	Moderate concerns about adequacy (-2): Data seemed fairly thin and came from just 2 studies	Low confidence (score: 6/12)

Patients reported that the treatment of TB and the effects of disease itself affected their ability to work. In addition to the loss of wages that this is associated with, as well as the subsequent financial hardship, patients described "feelings of 'uselessness' and being 'a burden' on their already struggling families."	Acha, 2007 Cramm, 2010 Gerrish, 2013 Reyes-Guillen, 2008	Moderate methodological limitations (-2): Unclear if 3 studies took the relationship between researcher and participants into consideration The approach to data analysis was unclear in 1 study The approach to sampling was unclear in 3 studies Limited provision of population characteristics (most notably site of disease) in all studies 1 study did not provide the number of patients included No study reported treatment regimen used Patient quotes not provided by/identified in 2 studies for this finding Evidence may not be from patients (family members) in 1 study	Moderate concerns about relevance (-2): No study was designed to directly examine the prioritisation of treatment outcomes Some concern over relevance of population: HIV status not described in 3 studies (national data suggested high prevalence in 1); 1 study HIV-negative	No concerns about coherence	Moderate concerns about adequacy (-2): The data was fairly thin and came from just 4 studies; there were few, if any, children included, and patients were all from poorer settings	Low confidence (score: 6/12)

Patients reported social impacts from the treatment and experience of disease. Some experienced feelings of social isolation (an isolation perhaps compounded by discrimination arising from the disease itself) because they lacked energy to join in with social activities, such as playing sports or drinking, or simply no longer felt like going out in public, making it difficult to maintain relationships.	Acha, 2007 Gerrish, 2013 Paz-Soldan, 2013	Moderate methodological limitations (-2): Unclear if 2 studies took the relationship between researcher and participants into consideration The approach to data analysis was unclear in 1 study The approach to sampling was unclear in 1 study Limited provision of population characteristics (most notably site of disease) in all studies 1 study did not provide the number of patients included No study reported treatment regimen used Patient quotes not provided by/identified in 2 studies for this finding Evidence may not be from patients (family members) in 1 study	Severe concerns about relevance (-3): No study was designed to directly examine the prioritisation of treatment outcomes Some concern over relevance of population: HIV status not described in 1 study (national data did not suggest high prevalence); 1 study HIV-negative; in another study 11 of 43 were HIV-positive (avoided extraction)	Moderate concerns about coherence (-2): Although patients reported that they experienced feelings of social isolation, other statements suggested friends and family were supportive, mitigating against the withdrawal of patients from social networks	Moderate concerns about adequacy (-2): Data neither particularly rich nor particularly thin; only 3 studies conducted in 2 cities	Very low confidence (score: 3/12)

The significance of 'cure' - in addition to its inherent desirability as a "way to stay alive and healthy" - was further enacted as a 'gatekeeper' to patients' returning to normal functioning, and even the possibility that they might "flourish".	Reyes-Guillen, 2008 Rundi, 2010 Zhang, 2010	Moderate methodological limitations (-2): Unclear if 1 study took the relationship between researcher and participants into consideration The approach to data analysis was unclear in 1 study The approach to sampling was unclear in 1 study Limited provision of population characteristics (most notably site of disease) in 2 studies No study reported treatment regimen used	Moderate concerns about relevance (-2): No study was designed to directly examine the prioritisation of treatment outcomes Some concern over relevance of population: HIV status not described in any of the studies (national data did not suggest high prevalence)	Mild concerns about coherence (-1): Although patients reported that they viewed antituberculosis treatment as a way to recover, which in turn was a step towards normal functioning and even flourishing, other statements demonstrated patients' fears that they will never sufficiently recover to achieve this; however, it is perhaps not surprising that such conflicts exist given the 'high stakes' of their situation	Mild concerns about adequacy (-1): Although data felt fairly thin in the varied descriptions of the phenomena, and it came from studies conducted only in poorer settings	Low confidence (score: 6/12)

The importance of adherence is also enacted as a 'gatekeeper', first to cure, then (as described above) to patients' returning to normal functioning, and even the possibility that they might "flourish".	Hu, 2008 Queiroz, 2012	Moderate methodological limitations (-2): Unclear if the relationship between researcher and participants was taken into consideration in either study Approach to analysis unclear in 1 study Approach to sampling unclear in 1 study Limited provision of population characteristics (most notably site of disease) in 1 study No study reported treatment regimen used Patient quotes not provided by/identified in 1 study for this finding	Moderate concerns about relevance (-2): No study was designed to directly examine the prioritisation of treatment outcomes Some concern over relevance of population: HIV status not described in 2 studies (national data did not suggest high prevalence)	Mild concerns about coherence (-1): Although patients reported that they viewed antituberculosis treatment as a way to recover and subsequently to return to normal functioning, which in turn provided greater motivation to adhere to treatment, other statements demonstrated a lack of trust in the power of treatment to make them healthy again or to keep them alive; however, it is perhaps not surprising that such conflicts exist given the difficulties experienced by many and the 'high stakes' of their situation	Moderate concerns about adequacy (-2): Data seemed fairly thin and came from just 2 studies	Low confidence (score: 5/12)

COMPARISON TO EXISTING REVIEWS OF TUBERCULOSIS TREATMENT

In order to examine the possible value of the review findings in relation to the study of the effectiveness of antituberculosis treatment, the outcomes identified as significant within the qualitative systematic review have been compared to those in Cochrane reviews of antituberculosis treatment and the reviews contained in the latest NICE guidance on TB treatment (2016).

COCHRANE REVIEWS OF TUBERCULOSIS TREATMENT

The Cochrane Database of Systematic Reviews was searched for Cochrane reviews and 'other reviews' published in English using a broad strategy of TB terms (Tuberculosis OR 'TB'). Papers that examined the pharmacological treatment of active TB in people without comorbidities or coexisting conditions that might affect the experience or management of their TB were included (see Table 7 for more details of the search). The search yielded 79 articles; full texts were retrieved for 9, and after exclusions (see Figure 6 for more details) 7 were included. See Appendix A for further details of exclusions.

The 7 included Cochrane papers (Bose *et al*., 2014; Davies *et al*., 2007; Gallardo *et al*., 2012; Gelbrand, 2000; Mwandumba and Squire, 2001; Rosa *et al*., 2012; Ziganshina and Titarenko, 2013) comprise 5 published reviews and 2 protocols of ongoing reviews. They covered a range of intervention questions, including the drugs used, the overall duration of treatment, frequency of dosing and the use of fixed-dose combinations versus single-drug formulations. The 5 published reviews reported a total of 22 primary studies. Table 12 summarises the relevant information within the Cochrane reviews.

Figure 6. Flow diagram of search and study inclusion process for Cochrane reviews of TB treatment

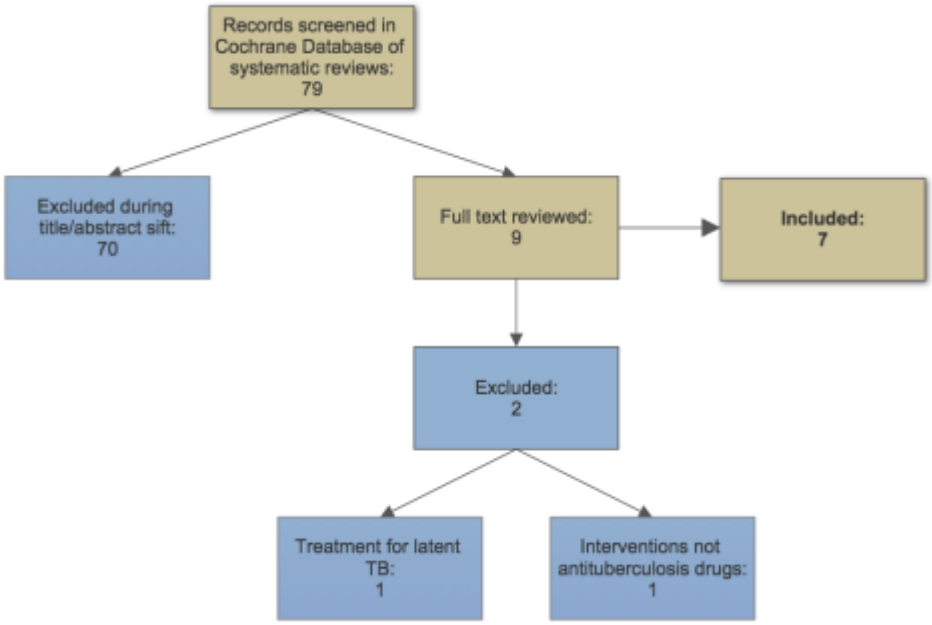


Table 12. Summary of Cochrane reviews of TB treatment

Review	*Status*	*Topic*	*Trials included (number; eligible designs)*	*Outcomes specified in review protocol*	*Included studies outcome reported in*
Bose et al., 2014	Published review	Intermittent, short-course antituberculosis regimens (twice- or thrice-weekly) daily short-course antituberculosis regimens in treating childhood TB	4 RCTs; quasi-RCTs	Cure (sputum smear and/or culture status, if available; resolution of signs and symptoms)	4
				Death from any cause	4
				Relapse	1
				Adherence	4
				Treatment-limiting adverse effects	4
Davies et al., 2007	Published review	Combination drug regimens containing rifabutin with those containing rifampicin for treating pulmonary tuberculosis	5 RCTs; quasi-RCTs	Cure (sputum culture status after completion of treatment)	2
				Relapse	2
				Sputum smear status	3
				Sputum culture status	2
				Adverse events (serious; leading to discontinuation of treatment; other)	4
Gallardo et al., 2012	Protocol	Fixed-dose combinations compared to single-drug	RCTs	A combined endpoint of treatment failure, relapse, or death.	n/a

		formulation for treating newly diagnosed pulmonary TB		Treatment failure (sputum culture status within 1 month of treatment completion)	n/a
				Relapse	n/a
				Mortality	n/a
Gelbrand, 2000	Published review	Regimens lasting less than 6 months compared with longer regimens in the treatment of active TB	7 RCTs	Relapse	7
				Adverse events (requiring interruption, alteration, or complete cessation of treatment)	2
				Cure (sputum culture status after completion of treatment)	3
				Mortality	0
Mwandumba and Squire, 2001	Published review	Rifampicin-containing short-course chemotherapy regimens, given two or three times a week, compared with similar regimens given daily in adult patients with pulmonary tuberculosis	1 RCTs; quasi-RCTs	Cure (sputum culture status within 1 month of treatment completion)	1
				Mortality	1
				Sputum culture status at 2 months	1
				Recurrence	1
				Emergence of drug resistance	1
				Toxicity	1
	Protocol		RCTs	Relapse / recurrence	n/a

Rosa et al., 2012		TMC207 as a substitute or additional drug for treatment of drug-sensitive and MDR-TB		Culture conversion	n/a
				Smear conversion	n/a
				Mortality	n/a
				Adverse events	n/a
Ziganshina and Titarenko, 2013	Published review	Fluoroquinolones as substitute or additional components in antituberculosis drug regimens for drug-sensitive TB	5 RCTs	Treatment failure (sputum culture status within 2 months of treatment completion)	1
				Relapse	1
				Combined endpoint: treatment failure and relapse	0
				Mortality	5
				Sputum culture or smear conversion	5
				Adverse events (fatal, life-threatening, requiring hospitalization, or change of treatment regimen)	5

REVIEWS OF TUBERCULOSIS TREATMENT IN THE 2016 NICE GUIDANCE

13 evidence reviews related to the drug treatment of active tuberculosis were identified within NICE's latest guidance on the prevention, diagnosis and management of TB, as well as the organisation of services, in the UK (2016). They covered a range of intervention questions, including the overall duration of treatment, frequency of dosing and the use of fixed-dose combinations versus single-drug formulations. The 13 reviews reported a total of 32 primary studies, though some of these were not directly relevant to the patient population of interest due to the inclusion of people with HIV. Table 13 summarises the relevant information within the reviews conducted by NICE.

Table 13. Summary of reviews of TB treatment in the 2016 NICE guidance

Topic	*Trials included (number; eligible designs)*	*Outcomes specified in review protocol*	*Included studies outcome reported in*
Fixed dose combination tablets with single-drug formulation regimens in the treatment of people with active tuberculosis	2 RCTs	Sputum conversion*	2
		Relapse*	1
		Treatment failure*	1
		Cure*	1
		Adherence*	2
		Adverse effects ('complaints')*	2
Intermittent dosing regimens and daily drug treatment regimens in children and young people with active tuberculosis	5 RCTs; quasi-RCTs; non-randomised controlled trials	Mortality	2
		Cure, treatment success and treatment failure	0
		Relapse	5
		Adverse events (that are severe enough to require a modification, interruption or discontinuation of treatment)	3
		Changes in the signs and symptoms of TB	4
		Adherence to treatment	2

		Emergence of acquired drug resistance	0
Intermittent dosing regimens and daily drug treatment regimens in adults with active tuberculosis	2 RCTs	Culture status*	1
		Treatment failure*	1
		Mortality*	1
		Adherence*	1
		Relapse*	1
		Adverse events*	1
Duration of treatment in adults with active pulmonary tuberculosis	12 RCTs; quasi-RCTs	Mortality	1
		Cure, treatment success and treatment failure	8
		Relapse	11
		Adverse events (that are severe enough to require a modification, interruption or discontinuation of treatment)	5
		Changes in the signs and symptoms of TB	3
		Adherence to treatment	3

		Emergence of acquired drug resistance	0
Duration of treatment in children and young people with active pulmonary tuberculosis	1 RCTs; quasi-RCTs; non-randomised controlled trials	Mortality	0
		Cure, treatment success and treatment failure	0
		Relapse	1
		Adverse events (that are severe enough to require a modification, interruption or discontinuation of treatment)	1
		Changes in the signs and symptoms of TB	0
		Adherence to treatment	1
		Emergence of acquired drug resistance	0
Duration of treatment in people with active CNS tuberculosis	2 RCTs; quasi-RCTs; non-randomised controlled trials, prospective cohorts	Mortality	1
		Cure, treatment success and treatment failure	0
		Relapse	1
		Adverse events (that are severe enough to require a modification, interruption or discontinuation of treatment)	1
		Changes in the signs and symptoms of TB	2
		Adherence to treatment	0

		Emergence of acquired drug resistance	0
Duration of treatment in people with active pericardial tuberculosis	0 RCTs; quasi-RCTs; non-randomised controlled trials, prospective cohorts	Mortality	n/a
		Cure, treatment success and treatment failure	n/a
		Relapse	n/a
		Adverse events (that are severe enough to require a modification, interruption or discontinuation of treatment)	n/a
		Changes in the signs and symptoms of TB	n/a
		Adherence to treatment	n/a
		Emergence of acquired drug resistance	n/a
Duration of treatment in people with active disseminated (including miliary) tuberculosis	0 RCTs; quasi-RCTs; non-randomised controlled trials, prospective cohorts	Mortality	n/a
		Cure, treatment success and treatment failure	n/a
		Relapse	n/a
		Adverse events (that are severe enough to require a modification, interruption or discontinuation of treatment)	n/a
		Changes in the signs and symptoms of TB	n/a
		Adherence to treatment	n/a

		Emergence of acquired drug resistance	n/a
Duration of treatment in people with active spinal tuberculosis	2 RCTs; quasi-RCTs; non-randomised controlled trials	Mortality	1
		Cure, treatment success and treatment failure	0
		Relapse	1
		Adverse events (that are severe enough to require a modification, interruption or discontinuation of treatment)	2
		Changes in the signs and symptoms of TB	2
		Adherence to treatment	0
		Emergence of acquired drug resistance	0
Duration of treatment in people with active lymph node tuberculosis	4 RCTs; quasi-RCTs; non-randomised controlled trials	Mortality	0
		Cure, treatment success and treatment failure	1
		Relapse	2
		Adverse events (that are severe enough to require a modification, interruption or discontinuation of treatment)	3
		Changes in the signs and symptoms of TB	1
		Adherence to treatment	1

		Emergence of acquired drug resistance	0
Duration of treatment in people with active gastrointestinal tuberculosis	2 RCTs; quasi-RCTs; non-randomised controlled trials	Mortality	0
		Cure, treatment success and treatment failure	2
		Relapse	2
		Adverse events (that are severe enough to require a modification, interruption or discontinuation of treatment)	1
		Changes in the signs and symptoms of TB	0
		Adherence to treatment	0
		Emergence of acquired drug resistance	0
Duration of treatment in people with active bone and joint (nonspinal) tuberculosis	0 RCTs; quasi-RCTs; non-randomised controlled trials	Mortality	n/a
		Cure, treatment success and treatment failure	n/a
		Relapse	n/a
		Adverse events (that are severe enough to require a modification, interruption or discontinuation of treatment)	n/a
		Changes in the signs and symptoms of TB	n/a
		Adherence to treatment	n/a

		Emergence of acquired drug resistance	n/a
Duration of treatment in people with active genitourinary tuberculosis	0 RCTs; quasi-RCTs; non-randomised controlled trials	Mortality	n/a
		Cure, treatment success and treatment failure	n/a
		Relapse	n/a
		Adverse events (that are severe enough to require a modification, interruption or discontinuation of treatment)	n/a
		Changes in the signs and symptoms of TB	n/a
		Adherence to treatment	n/a
		Emergence of acquired drug resistance	n/a
* Review undertaken as part of an older piece of guidance; NICE methodology at the time did not require reviewers to specify the outcomes of interest *a priori* in the review protocol, reviewers simply extracted and synthesised available outcome data			

COMPARISON OF QUALITATIVE REVIEW FINDINGS TO INTERVENTION REVIEWS OF TB TREATMENT

The qualitative systematic review of patient perspectives on the outcomes of TB treatment and their relative significance identified the improvement of the signs and symptoms of disease, mortality and survival, treatment failure, success and cure, adverse effects of treatment and the impact of treatment on a patient's ability to function or flourish in life as important. Their presence in the 7 identified Cochrane reviews of TB treatment and the 13 reviews of TB treatment within the 2016 NICE guidance on TB are summarised in Table 14.

Improvement in the signs and symptoms of disease was specified as an outcome of interest in just 1 Cochrane review. In Bose et *al*. (2014)'s investigation of dosing frequency in children, the improvement in the signs and symptoms of disease was captured within their definition of 'cure':

> *"including the following:*
>
> - *negative sputum test (if appropriate);*
> - *weight gain;*
> - *resolution of symptoms and signs within one month after completion of treatment. These may include, but are not confined to:*
>   - *fever or cough,*
>   - *decrease in size of the lymph nodes, and*
>   - *resolution of the chest X-ray findings."*

This is also reflected within the 'response to treatment' outcome included in the NICE reviews of dosing frequency in children and young people with active tuberculosis. Obtaining sputum samples from small children is particularly difficult and the disease is often paucibacillary, therefore obtaining an accurate diagnosis of pulmonary disease – or its cure – can be difficult if relying on microbiological diagnosis alone (Shingadia and Novelli, 2003). Consequently, clinical criteria based on the presence or absence of the signs and symptoms of disease are often used in addition to sputum smear and/or culture in children with suspected pulmonary TB. For this reason – that the inclusion of the outcome is about classifying the patient as a 'cure' rather than about the alleviation of the patient's symptoms and the associated burden of disease, and that this inclusion was in combination with sputum smear and/or culture status – it is not possible to say that the outcome identified as significant to patients has truly been reported, not in the manner that it was identified as significant in the qualitative evidence synthesis.

Improvement in the signs and symptoms of disease was specified as an outcome of interest in 11 of the 13 reviews of TB treatment undertaken by NICE (84.6%), although it was found that just 42.9% of the included primary studies reported data for this outcome.

Mortality was specified as an outcome of interest in 6 Cochrane reviews (85.7% of the identified reviews). However, it was reported in just 10 (58.8%) of the primary studies included within these reviews. The inclusion of mortality as an outcome of interest in the NICE reviews was somewhat higher – 12 reviews (92.3%) – yet only 20% of the included studies reported data for it. Mortality in these studies and reviews covered a range of measures, including all-cause mortality and TB-related deaths.

Treatment failure, success and cure was also specified as an outcome of interest in 6 Cochrane reviews (85.7% of the identified reviews) and 13 (100%) of the reviews conducted by NICE. It was reported in just 50% of the primary studies included within the Cochrane reviews and 43.8% of the studies in the NICE reviews.

Furthermore, there were inconsistencies in the definitions used. A range of measures were used to classify the outcome, including: sputum smear and/or culture status in combination with signs and symptoms of disease; sputum culture status after completion of treatment; sputum culture status within 1 month of treatment completion; and sputum culture status within 2 months of treatment completion.

The adverse effects of treatment was specified as an outcome of interest in 6 Cochrane reviews (85.7% of the identified reviews) and reported in 16 (72.7%) of the primary studies included within these reviews. They were an outcome of interest in all of the NICE reviews, but reported in just 59.4% of the studies these reviews included.

The adverse events of interest varied from review to review, and included those requiring interruption, alteration, or complete cessation of treatment, those leading to hospitalisation or continuation of hospitalisation, those that led to persistent or significant disability, and those could be attributed to a specific component of the antituberculosis regimen. The specific adverse events reported included hepatotoxic, hypersensitivity, cutaneous, gastrointestinal and haematologic reactions.

And finally, the impact of antituberculosis treatment on the functioning (or flourishing) of the patient, whether in social, physical, developmental, educational or economic terms, was not specified by any of the reviews; for this reason, it is not clear whether or not it has been investigated in any primary studies of TB treatment.

Table 14. Incidence of identified patient-important outcomes

Outcome identified as significant to patients	***Cochrane reviews of TB treatment (n = 7)***		***Reviews of TB treatment in the 2016 NICE guidance (n = 13)***	
	Reviews of TB treatment in which outcome specified or reported (% of reviews)	*Included primary studies treatment outcome reported in (% of included studies within reviews where it was specified)*	*Reviews of TB treatment in which outcome specified or reported (% of reviews)*	*Included primary studies treatment outcome reported (% of included studies within reviews where it was specified)*
Improvement in the signs and symptoms of disease	1 (14.2%)*	4 (100%)*	11 (84.6%)	12 (42.9%)
Mortality and survival	6 (85.7%)	10 (58.8%)	12 (92.3%)	6 (20.0%)
Treatment failure, success and cure	6 (85.7%)	11 (50%)	13 (100%)	14 (43.8%)
Adverse effects of treatment	6 (85.7%)	16 (72.7%)	13 (100%)	19 (59.4%)
Impact on functioning	0	n/a	0	n/a

* note: included in combination with sputum smear and/or culture status as part of a composite classification of ‘cure’

Exploring the use of qualitative systematic reviews in the development of core outcome sets: could they increase the volume and diversity of patient perspectives included?

THE VOLUME AND DIVERSITY OF PATIENT PERSPECTIVES INCLUDED IN CORE OUTCOME SETS

In order to examine the possible value of qualitative systematic reviews of patient perspectives on treatment outcomes in relation to COS development, the volume and diversity of the patient sample in the qualitative systematic review of patient perspectives on TB and its treatment are presented and compared to the volume and diversity of patient perspectives included within qualitative studies used in the development of COS and registered in the COMET Initiative database (http://www.comet-initiative.org/studies/search).

The characteristics of patients included in the qualitative evidence synthesis of perspectives of TB and its management are summarised in Table 15.

Table 15. Population characteristics of patients included in the qualitative systematic review of perspectives of TB and its management

Study	***Country***	***Number of patients included***	***Age***	***Sex***	***National incidence of TB in 2014 (WHO, 2015)****	***Socioeconomic level***	***Education***	***Occupation***
Acha *et al.*, 2007	Peru	-	-	-	High	Mid	-	-
Bennstam *et al.*, 2004	Democratic Republic of Congo	24	Adults	13 female and 11 male	High	Low/very low	-	-
Cramm *et al.*, 2010	South Africa	67	Adults	35 female and 32 male	High	Low	61 (91.0%) some formal education	17 employed (25.4%)
Dias *et al.*, 2013	Brazil	15	Adults	-	High	Mid/low	1 (6.7%) illiterate; 4 (26.7%) 1-7 years; 10 (66.7%) ≥8 years	8 53.3%) employed, 4 (26.7%) retired, 2 (13.3%) studying, and 1 (6.7%) unemployed
Franck *et al.*, 2014	South Africa	20 children, supplemented with interviews with caregivers	Children	-	High	Mid	-	-

Gerrish *et al.*, 2012 Gerrish *et al.*, 2013	UK	14	-	5 female and 9 male	Moderate	High/mid	-	-
Hu *et al.*, 2008	China	33	-	-	High	Low	-	-
Khan, 2012	India	25	-	15 female and 10 male	High	Very low	-	-
Mafigiri *et al.*, 2012	Uganda	107	Adults	48 female and 59 male	High	Very low	-	-
Naidoo *et al.*, 2009	South Africa	15	Adults	males and females included, though split not reported	High	Low/very low	1 completed grade 12; 8 secondary schooling, 4 primary schooling, 1 below-grade-2 qualification	10 were not engaged in gainful employment
Paz and Sá, 2009	Brazil	21	Adults	-	High	Mid	-	-
Paz-Soldan *et al.*, 2013	Peru	43	16 children, 27 adults	-	120 per 100 000 population High	Mid	-	-

Queiroz *et al.*, 2012	Brazil	4	Adults	2 female and 2 male	High	High/mid	studied 7.7 years on average	1 was formally employed, 1 temporary job, 2 unemployed; all reported depending on their families for financial support
Reyes-Guillen *et al.*, 2008	Mexico	8	Adults	1 female and 8 male	Moderate	Low/very low	4 no schooling; 1 completed primary school; 1 3rd grade; 1 high school; 1 university	2 unskilled labourors, 1 primary school teacher, 1 office worker, 1 worker, 1 peasant, 1 household chores, 1 driver; none working at time of study
Rundi, 2010	Malaysia	27	Adults	12 female and 15 male	High	Low	-	7 farmers, 6 housewives, 2 retirees, 4 unemployed , 4 self employed, 4 'other'
Sagbakken *et al.*, 2008	Ethiopia	32	9 <25 years; 23 >26 years	16 female and 16 male	High	Mid	7 partly illiterate/illiterate; 9 1-6 years schooling; 7 7-10 years; 9 11-13 years	8 daily labourers, 6 civil servants, 9 private sector workers, 9 'other'

Tadesse *et al.*, 2013	Ethiopia	26	>14 years	15 female and 11 male	High	Low	8% had secondary school qualifications	13 participants were not employed
Van den Boogaard *et al.*, 2012	Tanzania	11	Adults	5 female and 6 male	High	Low	7 had attended primary education only; 3 had completed secondary school, and 1 had no formal education	-
Van Elsland *et al.*, 2012	South Africa	11	Children	-	High	Low	4 children were attending school at the time of the study; all caretakers had completed 6–12 years of schooling	-
Xu *et al.*, 2009	China	20	-	5 female and 15 male	High	Mid	-	-
Zhang *et al.*, 2010	China	17	2 <20 years; 15 ≥20 years	5 female and 12 male	High	Low	University students	University students

Zuñiga *et al*., 2014	US (US-Mexico border)	18	Adults	5 female and 13 male	US: low Mexico: moderate	Low/very low	0 to 14 years of education	11 no job at the time of the interview; 1 participant maintained a job continuously during diagnosis and treatment, all the others had stopped working at some point during DOT, although 6 had since returned to work
* Low incidence defined here as ≤10 cases (all sites of disease) per 100,000 population; moderate incidence defined here as >10 to <40 cases (all sites of disease) per 100,000 population; high incidence defined here as ≥40 cases (all sites of disease) per 100,000 population								

By applying relevant filters (stakeholders involved were filtered by 'consumers (patients)' and 'service users', and publication year up to and including 2015 to ensure only published studies were retrieved), 65 papers were identified that described patient involvement in the development of COS (See Table 8 for further details of the search). 27 papers were excluded after screening at the title and abstract-level. After screening 38 papers at the full paper-level, 14 papers covering the development of COS for 7 conditions were included. The qualitative methods used for obtaining patient views included were focus groups and interviews. See Figure 7 for further details of the study selection process; see Appendix A for further details of exclusions. Table 16 summarises the relevant information from the included COS papers.

Figure 7. Flow diagram of search and study inclusion process for COS in which qualitative research of patient perspectives was used

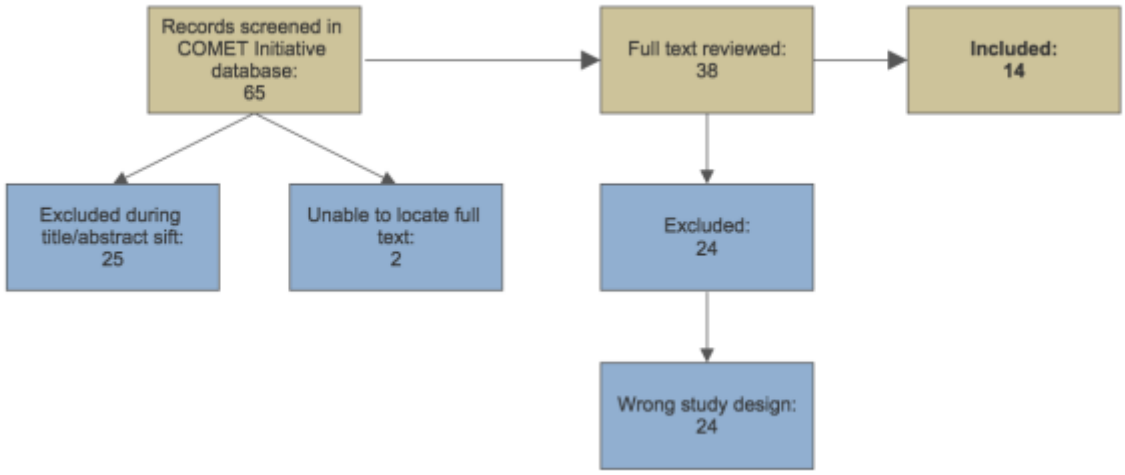


Table 16. Summary of qualitative studies of patient perspectives included in the development of core outcome sets

Condition	Study / studies	Methods used to collect patient views	Number of patients included	Geographical location	Age	Sex	Socioeconomic level	Education	Occupation
Cleft palate; otitis media	Tierney et al., 2015; Bruce *et al*., 2015	Semi-structured interviews and participatory techniques, including activities on a tablet computer, yielding field notes	22 patients aged 6 to 11; parents of 37 patients aged 0 to 11 years	UK	22 patients aged 6 to 11; parents of 37 patients aged 0 to 11 years	13 male and 9 female	-	-	-
Clinical genetics	McAllister *et al*., 2011	Interviews and focus groups	12	UK	-	-	-	-	-
	McAllister *et al*., 2008; McAllister *et al*., 2007; McAllister *et al*., 2007b	Interviews and focus groups	19	UK	-	-	-	-	-
End-stage kidney disease	Howell *et al*., 2012	Focus/nominal group technique	57	-	Adults	-	-	-	-

Fibromyalgia	Arnold *et al*., 2008	Focus groups	48	US	Adults	All female	-	6 (12.5%) high school; 35 (72.3%) college; 7 (14.6%) 'other'	19 (40%) in full-/part-time work
Neurodisability	Allard *et al*., 2014	Interviews and focus groups	54 patients; 53 parents	UK	8 to 25 years; parents of children aged 4 to 23 years	34 male and 20 female	1 (less deprived areas): 7 patients, 8 parents 2: 13 patients, 4 parents 3: 9 patients, 2 parents 4: 7 patients, 5 parents 5 (more deprived areas): 6 patients, 16 parents	-	-
Oral mucositis	Bellm *et al*., 2002	Focus groups	2	US	-	-	-	-	-
Rheumatoid arthritis	Sanderson *et al*., 2012	Interviews	16	UK	Adults	All female	-	1 did not finish primary school;7	-

								finished primary school; 2 finished secondary school; 6 went to university	
	Sanderson *et al*., 2010	In-depth interviews	23	UK	Adults	5 male and 18 female	-	-	-
	Carr *et al*., 2003	Focus groups	39	UK	Adults	-	-	-	-

Patient population sizes in the qualitative systematic review of patient perspectives of TB and TB treatment ranged from 4 to 107, though 1 study did not report the population size (Acha *et al*., 2007). The number of patients included in the synthesis overall was at least 558; the failure to provide the number of patients included in Acha *et al*. (2007) means that this pooled sample size is an underestimate.

The number of patients included in qualitative research that has been used in the development of COS ranged from 2 to 78.

The qualitative evidence synthesis of patient perspectives of TB and its management brings together 23 papers describing 22 studies conducted across 13 countries: 5 in Sub-Saharan Africa (the Democratic Republic of Congo, Ethiopia, South Africa, Tanzania, Uganda), 3 in Asia (China, India, Malaysia), 2 in South America (Brazil, Peru), 1 in Central America (Mexico), 1 in North America (the United States) and 1 in Europe (the United Kingdom).

The qualitative studies of patient perspectives included in COS to date have been conducted solely in the United Kingdom and in the United States.

See Figure 8 for the geographical spread of perspectives included.

Figure 7. Geographical spread of patient perspectives included in i) the qualitative systematic review of tuberculosis and its management, and the core outcome set qualitative literature for ii) cleft palate, iii) clinical genetics, iv) fibromyalgia, v) neurodisability, vi) oral mucositis, and vii) rheumatoid arthritis

i) Tuberculosis qualitative systematic review

ii) Cleft palate core outcome set

iii) Clinical genetics core outcome set

iv) Fibromyalgia core outcome set

v) Neurodisability core outcome set

vi) Oral mucositis core outcome set

vii) Rheumatoid arthritis core outcome set

Furthermore, the qualitative systematic review included research conducted across a broad range of disease incidence levels, from low (in the United States, with an incidence of just 3.1 cases per 100,000) to moderate (Mexico (21 cases per 100,000) and the United Kingdom (12 cases per 100,000)) to high (Brazil (44 cases per 100,000), China (68 cases per 100,000), Democratic Republic of Congo (325 cases per 100,000), Ethiopia (207 cases per 100,000), India (167 cases per 100,000), Malaysia (103 cases per 100,000), Peru (120 cases per 100,000), South Africa (834 cases per 100,000), Tanzania (327 cases per 100,000), Uganda (161 cases per 100,000)) (World Health Organization, 2015). Conversely, the COS developed for cleft palate, clinical genetics, fibromyalgia, neurodisability, oral mucositis, and rheumatoid arthritis included qualitative research from just the United States and the United Kingdom; this limited geographical is unlikely to translate into a breadth of incidence levels.

The age of participants was not reported in 3 of the COS studies. The patient population included in the cleft palate COS ranged in age from 0 to 11 years; although parents of children with cleft palate were included, no views of adult *patients* were sought. The patient population in the neurodisability COS ranged in age from 4 to 25 though, again, parents of patients were included. The COS studies for end-stage kidney disease, fibromyalgia and rheumatoid arthritis included only adults. By comparison, the qualitative systematic review enabled a diverse range of age groups (0 to 80 years, where reported) to provide perspectives on TB and its treatment.

Overall, 219 men and 182 women were reported within the qualitative systematic review (number not provided in 8 studies), showing both genders to have received a good level of consideration; two studies focused explicitly on the role of gender in women's experiences of TB.

5 COS studies did not report the sex of their patient populations. The studies for cleft palate and neurodisability had good representation of both sexes (in terms of the relative proportions included, as opposed to the absolute volume), whereas the COS for fibromyalgia and rheumatoid arthritis centred almost exclusively on women.

The socioeconomic characteristics were poorly reported in almost all of the qualitative studies examined, both in the COS papers and in the papers included in the qualitative systematic review. Where reported, there was a relatively diverse range of participants included, in terms of the level of education achieved and in the type of employment in which they were engaged (and in the levels of employment more generally). However, the paucity of information and inconsistency in the parameterisation of the socioeconomic characteristics where they *were* reported limited the extent to which comparison was possible.

Discussion

The qualitative systematic review of patient perspectives of TB and its treatment highlighted the following to be outcomes of significance to patients: improvement in the signs and symptoms of disease; mortality and survival; treatment failure, success and cure; the adverse effects of treatment; and the impact of treatment on the patient's ability to function (and flourish) in social, physical, developmental, educational or economic terms.

These outcomes were derived through the thematic synthesis of qualitative data extracted from 23 papers describing 22 studies conducted across 13 geographically and socioeconomically diverse countries. There was a lack of 'direct' evidence – that is, no study was designed and reported for the explicit purpose of patient prioritisation of antituberculosis treatment outcomes – which meant that this evidence synthesis required translation of the identified qualitative data into theories about outcomes. For this reason, the outcomes identified by the review as of possible importance to patients could not be simply extracted from the data: interpretation of data relating to phenomena such as patient experiences of TB treatment (including adherence to that treatment) and of TB services, as well as patient experiences of TB-related stigma, was required. More than this, the significance of these outcomes to patients was often enacted through these other phenomena.

Fear of TB being a deadly or incurable disease is well-documented in the literature (Auer *et al*., 2000; Demissie *et al*., 2003; Johansson *et al*., 2000; Karim *et al*., 2003; Long *et al*., 2001), lending support to the review findings that mortality and survival and treatment failure, success and cure are outcomes of potential significance to patients. Fear can also arise in relation to social or economic phenomena: for example, TB carries a risk of unemployment and can impair the chances of those with the disease finding and retaining a partner (Johansson *et al*., 2000) – a relationship that provides further support for this review's finding that the impact on a patient's ability to function (and flourish) in social, physical, developmental, educational or economic terms is an important treatment outcome.

TB has also been associated with the fear that a person with the disease puts those around them, including other family members, members of their household, or simply those they come into contact with, at risk of infection (Kelly, 1999). Furthermore, as noted by Juniarti and Evans (2011), fear can be "linked to the stigma and shame of having TB and the risk that others would find out that they had contracted the disease". Stigma can be defined in many ways:

> *"Stigma is considered to be a social process that gives a mark or attribute to individuals and is characterised by exclusion, rejection, blame or devaluation of that individual. [It can be described] as a social disgrace that results from a transformation of the body, blemish of the character or*

> *membership of a despised group and that it disqualifies the bearer from full social acceptance. It has also been described as labelling, stereotyping, separation, status loss and discrimination." (Juniarti and Evans, 2011)*

Fear is both a manifestation and driver stigma, but represents just one feature of the stigma encountered by people with TB or their families. For example, Juniarti and Evans 2011 systematic review, which incorporated 30 qualitative studies of patients' experiences of stigma, also highlighted the experience of shame and isolation. Shame – or "what people felt as a consequence of having TB because it was considered to be a bad disease, … a disease that people wanted to conceal from their family, friends and community" – was evident in nearly all of the studies included in the review:

> *"The theme of shame that emerges from these studies highlights the widely held view that TB is a 'dirty' disease, a disease that should remain the secret of the person with TB, perhaps even from their family. For individuals and families, the shame relates to the embarrassment of having a disease associated with immoral practices and bad behaviour and the resulting loss of social status." (Juniarti and Evans, 2011)*

Isolation, or diminished social contact, was found to arise through both withdrawal by the people with the disease themselves from friends, family or the wider community due to the fear of transmission to others or a concern for the treatment they might receive from others, but also a shunning by those around them (Baral, *et al*., 2007; Hansel, *et al*., 2004; Kelly, 1999; Liefooghe, *et al*., 1997). Such isolation was reported to extend beyond treatment completion, even when the disease was cured (Atre *et al*., 2004; Balasubramanian *et al*., 2004; Baldwin *et al*., 2004; Bennstam *et al*., 2004; Godfrey-Faussett *et al*., 2002; Jaramillo, 1999; Johansson *et al*., 2000; Karim *et al*., 2003; Kelly, 1999; Khan *et al*., 2000; Liefooghe *et al*., 1997; Long, *et al*., 2001; Meulemans, *et al*., 2002; Xu *et al*., 2004; Zhang *et al*., 2007). This provides a degree of support to this review's finding that cure is a treatment outcome of importance to patients, though of perhaps greater significance is its highlighting of the need for improved efforts in patient and community education.

Further to their association with fear and stigma, all of the outcomes had the potential to interact with a patient's adherence to their treatment regimen, demonstrating – in addition to their significance as treatment outcomes that should be measured in trials of antituberculosis regimens – their potential role as barriers or enablers of successful treatment completion. This was explicitly evident in the underpinning evidence for all of the outcomes highlighted as of potential importance to patients in the review findings. This is consistent with other qualitative TB literature, as demonstrated in Munro *et al*.'s 2007 systematic review of 44 studies examining the barriers and enablers to achieving or antituberculosis treatment adherence. For example, a theme identified within the literature as 'interpretations of illness and wellness' highlighted the

impact of symptom relief, adverse effects from treatment and beliefs about cure as interacting with adherence:

> *"Studies in our synthesis reported that patients stopped treatment because they felt better and thought that they were cured or because their symptoms abated. Some studies noted that patients who felt worse than before treatment or saw no improvement in their condition might be more likely to interrupt treatment." (Munro* et al*., 2007)*

Another theme entitled 'knowledge, attitudes, and beliefs about TB treatment' also highlighted the affect patient views on the effectiveness of treatment in curing TB, with one patient declaring, "No doctor is able to cure this", and another, "When you take medications, these bugs will die, he told me. The medications kill the bugs. This is what I've been told, but I'm not sure. It seems uncertain to me. Because the pills didn't help me." (Munro *et al*., 2007). The 'influence of side effects' was yet another relevant theme identified in the qualitative studies reviewed by Munro *et al*. which resonates with the findings of the present review, as did the theme 'financial burden of TB treatment'. A range of studies in the review suggested that TB had consequences for work, with a number of these supporting this review's assertion that the impact of treatment on the patient's ability to function (and flourish) in economic terms is of importance to patients. For example, one patient stated that "We cannot remain out of a job for long. As soon as we feel better we would like to go to work… If I cannot earn, my whole family will suffer" (Munro *et al*., 2007). In addition to being of potential importance to patients, it is critical that these drivers and barriers to adherence are considered within clinical research because they are inextricably linked to the achievement of treatment success and the enhancement of patient quality of life.

A person's quality of life is affected by "the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment" (World Health Organisation, 1997). These 'domains', as they are termed in the formal assessment of quality of life, align closely to the outcomes highlighted by this review, even in their statement in the abstract. Rooting them in the literature, in the assessment of quality of life amongst people with TB, studies have found the domains most affected by the disease to be the physical and the psychological (Dhuria *et al*., 2008). The psychological, as discussed above, is likely to result from the uncertainty, fear and stigma associated with the disease, in which all of the outcomes identified by this review might play a role. The physical is likely enacted through suffering brought about by not only the disease itself (the signs and symptoms of disease) but also by its treatment (its adverse effects). The disease carries with it a range of symptoms of varying severity, the most common being cough, the coughing up of blood, chest pain, fever, chills, night sweats, appetite and weight loss, malaise and easy susceptibility to physical and mental exhaustion (Kapplan *et al*., 2009). The treatment of active tuberculosis disease, even in patients with drug susceptible disease, carries a range of possible side effects which might adversely affect a person's quality of life. These include cutaneous reactions, typically flushing and itching with or without a rash, gastrointestinal

reactions, including nausea, vomiting, anorexia, abdominal discomfort, constipation and diarrhoea, 'flu syndrome (fever, chills, headache, dizziness, and bone pain), shortness of breath and wheezing, and peripheral neuropathy, hepatitis, and renal failure (Rifinah – Summary of Product Characteristics (SPC) – Emc). These affects can – as highlighted in the present review – sometimes be "as severe or more severe" than the disease itself, and in the case of hepatitis and renal failure can even lead to death. It seems intuitive that such clear harms to a patient's quality of life should constitute part of a core outcome set for TB.

There were some juxtapositions within the findings that at first glance might appear to be contradictions: the view of treatment as a "way to stay alive and healthy" and the doubt that many patients felt that treatment could cure them completely or that they would survive the "deadly disease" (Dias *et al.*, 2013), for example. However, when considered within the difficult situation in which patients find themselves – in which hearsay, personal experience or historical views of TB have instilled fear amongst patients and wider communities, in which a patient may have available to them a number of choices but none 'easy' or 'risk-free' since the treatment can be associated with as many burdens, harms and losses as the disease itself – it is perhaps not surprising that such strong and apparently conflicting perspectives endure amongst patients.

Such complexity in patients' experiences and views of TB and its treatment is also demonstrated by the overlap and interconnectedness between the outcomes identified. For example, the significance of symptom relief arises, to some extent, through its association with treatment success. The patient quoted below, for example, uses weight gain as a surrogate for recovery and survival:

> *"You go to the Health Center every day to check your weight. If it's not higher than last time, you will ask yourself why and be afraid that your treatment will not bring recovery. You will ask yourself: Will I recover or die?" (patient quote; Bennstam* et al.*, 2004)*

In another example, patients reported that there was a causal link between social isolation or the impairment of their ability to work and earn money – two domains that constitute the 'impact on functioning' outcome – and their response to treatment, both in terms of treatment success and in terms of any adverse effects experienced:

> *"Everything will be difficult for me, if I could not be cured. Maybe I will not be employed." (patient quote; Zhang* et al.*, 2010)*
>
> *"Others mentioned that the medications made them feel so queasy and tired that they no longer felt like going out in public." (Paz-Soldan* et al.*, 2013)*
>
> *"The social impact of their illness over a prolonged period of time was notable. Patients found it hard to maintain social networks. Two patients were unable to continue in employment and loss of income as well as*

> *status was distressing ... [Some] patients reported that their initial experience of social isolation reduced once they made known that they were responding well to treatment." (Gerrish* et al*., 2013)*

In this way, the significance of treatment success and cure was enacted not solely as a means of staying alive and healthy, but as a gatekeeper to patients' ability to function or flourish.

In identifying these intricacies within the views of TB patients, a context and richness to the importance of different outcomes has been obtained in a manner that may have been missed through the use of quantitative social research methods (surveys or consensus techniques, for example) alone. This represents part of the potential value in conducting systematic reviews of qualitative evidence as part of COS development.

The confidence in these review findings ranged from moderate to very low, though the most prevalent level of confidence was low. This means that, on the whole, "it is possible that the review finding[s were] a reasonable representation of the phenomen[a] of interest" (Lewin *et al.* (2015)); that is, "it is possible" that the treatment outcomes identified were outcomes that were important to patients which should be considered within the development of a COS for tuberculosis.

There were consistent issues with the adequacy of the data underpinning each of the identified themes and subsequent outcomes, both in terms of the richness of the data and its quantity, meaning that theoretical saturation was not achieved. Additional data, preferably from focus groups and interviews designed specifically with the objectives of COS development in mind, would be valuable verifying – or 'triangulating' – review findings.

The poor reporting of both the research methods and of relevant participant quotes was notable across almost all of the included studies. As Atkins *et al.* noted in their qualitative systematic review of adherence to tuberculosis treatment,

> *"Appraising the studies became an exercise in judging the quality of the written report rather than the research procedure itself … Papers appearing to have face validity, and that we intuitively felt to be well conducted research, did not necessarily come across as such in our quality assessment." (2008)*

In addition to the lack of supporting patient quotes for some review findings, key information that was consistently under-reported included population characteristics, the approach to sample recruitment, and details of data collection and analysis (including consideration of the role of the researcher and their relationship to the participants). Without this information it cannot be possible for a reviewer to fully evaluate the reliability and relevance of the evidence in question, nor can the reviewer be fully confident in the subsequent interpretation of the evidence and in the conclusions they draw.

There were also consistent issues with the relevance of the population (generally arising from the inclusion of patients with comorbidities or coexisting conditions that might affect their experience of the disease and it management – most notably HIV) and the relevance of the phenomena under study. This last point – that no studies were designed explicitly with outcome prioritisation in mind – shows that the phenomenon has yet to be clearly conceptualised in the literature, reflecting the novelty of the research question. The evidence was, in general, only indirectly relevant to the research question and 'concealed' within a myriad of irrelevant study findings. Furthermore, there may be an impact on the relevance of the included evidence on other levels because the design and reporting of the studies are themselves less relevant – for example, in terms of their approach to sampling, the data presented or frameworks used for analysis.

There was a variation across the outcomes identified as important to TB patients in terms of their specification within the review protocols for Cochrane and NICE reviews of drug treatment for active TB disease. Whilst mortality and survival, treatment failure, success and cure and the adverse effects of treatment were specified in almost all of the reviews, the improvement in the signs and symptoms of TB was expressed in just 1 (14%) of the Cochrane reviews but in 11 (85%) of the reviews conducted by NICE. The impact of treatment on a patients' potential 'to function' – whether in social, physical, developmental, educational or economic terms – was not specified in any review. The overall confidence in this broad review finding was moderate; that is, in accordance with the CERQual definition, it is considered likely that the review finding is a reasonable representation of the phenomenon of interest. As such, it is the review finding in which the reviewer had the most confidence, and is a review finding which is well-supported by other TB literature (see above discussion). This makes its absence from the NICE and Cochrane reviews all the more noteworthy.

That NICE's reviews were better representative of patient views on outcome prioritisation is perhaps explained by the greater inclusion of patients in their development process. Not only does the methods manual instruct developers to consider "What is really important for people using services?" when they are choosing the outcomes that will be included within their reviews, but the review protocols are developed in conjunction with – then signed off by – committees that include patient and other lay members (NICE, 2014):

> *"All Committees have at least 2 lay members with experience or knowledge of issues that are important to people using services, family members and carers, and the community affected by the guideline. This helps to ensure that the guideline is relevant to people affected by the recommendations and acknowledges general or specific preferences and choice." (NICE, 2014)*

When the primary studies included within the NICE and Cochrane reviews were examined for the reporting of outcomes identified as important to patients, the success rate was much lower, even for mortality and survival, treatment failure, success and cure and the

adverse effects of treatment. Just 20% of papers within the NICE reviews that specified it and 59% of papers within the Cochrane reviews that specified it reported data for mortality or survival. Just 44% of papers within the NICE reviews that specified it and 50% of papers within the Cochrane reviews that specified it reported data for treatment failure, success and cure. And just 59% of papers within the NICE reviews that specified it and 73% of papers within the Cochrane reviews that specified it reported data for the adverse effects of treatment.

The failure of trials to report outcomes that are potentially significant to patients is also evident in a systematic review of outcomes reported in phase II studies of newly-diagnosed pulmonary tuberculosis (Bonnett and Davies, 2015). The publication of this review solely as a conference abstract precluded the necessary detail for it to be used in a more comprehensive comparison with those outcomes identified in the qualitative evidence synthesis. However, this review found the most commonly reported outcomes to be early bactericidal activity, CFU count and culture status at 8 weeks of treatment or less. As noted by the GRADE Working Group, "when important outcomes are relatively infrequent, or occur over long periods of time, clinical trialists often choose to measure substitutes, or surrogates, for those outcomes" (Guyatt *et al*., 2011). It is unlikely that these microbiological outcomes would be directly meaningful to patients' decision-making about treatment, and could instead be considered surrogates for more downstream, patient-important outcomes such as treatment failure, success and cure.

The text cited above from Guyatt *et al.* (2011) may provide some explanation more generally for the scantiness of the identified patient-important outcomes in many of the clinical trials identified in the Cochrane and NICE reviews. Outcomes such as mortality and effects on patient function *are* relatively infrequent or occur in relatively small numbers over long periods of time. Trials with long periods of follow-up and large sample sizes are necessary to detect significant differences in these outcomes, and these are highly resource intensive. With a condition such as TB – whose treatment is generally a minimum of 6 months – even the measurement of cure rates requires studies of longer duration.

When compared to the patient populations within primary qualitative studies registered on the COMET Initiative's COS database, the qualitative evidence synthesis far surpassed the current COS literature in terms of the number of patients included, the geographical coverage, the range of age groups and the proportion of men and women included.

The review of the COS literature also showed there to be a paucity of in-depth qualitative studies providing rich descriptions of patient perspectives included in current COS research, suggesting that there may be potential for the use of qualitative evidence synthesis to systematically generate theory about outcomes that may be important to patients from indirect sources of data. It is important to incorporate as much existing knowledge and evidence as possible (the idea of 'wasting' information goes against the principles of evidence-based decision-making); however, it would also be important to consider whether this is a more critical use of resources than conducting primary qualitative studies that directly study patient views on treatment outcome prioritisation.

A notable failure of the evidence synthesis in terms of outcome *prioritisation* is that no 'ranking' of the outcomes was possible based on any explicit statement of their relative importance to patients. Despite this, these outcomes – and the context and detail that the review findings afford them – may provide useful resources should COS-specific patient focus groups or interviews eventually be undertaken.

The search for and synthesis of a broader array of evidence theoretically allows a greater volume and diversity of patient perspectives to be considered in the development of a COS. This is because, firstly, the literature has been systematically searched for using an inclusive search strategy, ensuring that as many potentially relevant papers as possible are identified. Secondly, the inclusion of more 'indirect' evidence means that a greater number and range of patients can be involved, although a degree of interpretation of the evidence is need with this approach. This diverse volume of perspectives can then be systematically pooled using qualitative evidence synthesis to give coherent, transparent theory about outcomes that are important to a broad range of patients. Triangulation of findings from individual studies using qualitative evidence synthesis will enhance the validity of the conclusions made, and allow the transferability of findings to be tested across a range of populations and contexts. This is important in the development of COS, which should be applicable to *all* populations and contexts in which the condition of interest arises.

STRENGTHS AND LIMITATIONS OF THE RESEARCH

The research was undertaken by a single reviewer, despite the acknowledgement that a minimum of two reviewers at the sifting, extraction and analysis stages is preferable when undertaking systematic reviews. The involvement of two reviewers, preferably from diverse disciplinary backgrounds, provides an "opportunity to discuss judgements" and "offer alternative interpretations" (Lewin *et al*., 2015).

> *"Readers of research reports bring to these texts a dynamic and unique configuration of experiences, knowledge, personality traits, and sociocultural orientations. Readers belong to one or more "interpretive communities" … that strongly influence how they read, why they read, and what they read into any one text. The members of these communities differ in their access and attunement to, knowledge and acceptance of, and participation with, for example, references and allusions in a text, the varied uses of words and numbers, and various genres or conventions of writing. Because of their varying reading backgrounds, experiences, and expectations, readers will vary in their interaction with texts." (Sandelowksi and Barosso, 2002)*

Arguably, this is particularly applicable in the case qualitative systematic reviews where the decisions made at each stage of the review and synthesis process can be more subjective than

for quantitative reviews due to the need for interpretation. Over-interpretation or inconsistent interpretation of the qualitative research is one of the main criticisms against qualitative synthesis.

Another weakness of the chosen research design is the inherently time-consuming nature of qualitative systematic reviews. As described previously, developing sensitive and precise search strategies for qualitative evidence is challenging and, unlike with quantitative systematic reviews, sifting at the title and abstract level is of limited efficacy in deciding the relevance of a paper. In both sifting and data extraction, the reviewer must immerse themselves more deeply in the text to assess the relevance of each paper and identify data applicable to the review question. This is even more true given the decision to include a broader range of evidence that was not produced with the same objectives as the review (the prioritisation of treatment outcomes). As stated above, this meant that information that might inform the review was often hidden amongst copious amounts of irrelevant information that required interpretation before its inclusion or exclusion could be confirmed. It was also found that this process was iterative, with papers having to be reviewed more than once before a definitive decision was made. This was further complicated by the fact that many studies were conducted in patient groups for whom indigenous knowledge is utilised as much as or more than biomedical knowledge, which presented further difficulties for interpretation.

The comparison of the review findings to the current TB literature would have benefited from a comparison not solely to the outcomes specified and reported in existing systematic reviews (that is, those conducted by Cochrane and by NICE) but to the wider, primary clinical trial literature. Undertaking a full review of the outcomes used in existing clinical trials of antituberculosis treatment would have enabled a fuller understanding of the review findings in the context of current practice, allowing a more nuanced evaluation of the gaps in current trial design and reporting. However, time and resource implications precluded the reviewer from undertaking this more detailed review of the current TB literature.

There are several important strengths to this research. To the author's knowledge, this is the first application of qualitative evidence synthesis to outcome prioritisation for COS development and as such provides new methodological ground for future research. It has provided a possible means of increasing the volume and diversity of the perspectives included in COS development, and it has systematically and in an evidence-based manner generated new theory on what constitutes patient-important outcomes for TB and demonstrated the failure of previous effectiveness research to consistently report these. This information can be used to inform future clinical trials. The CERQual assessments performed mean that those planning such trials – and other end users of the review – can interpret the findings in the context of a rigorous assessment of the confidence that should be placed in each.

The research has also, however, highlighted the need for primary qualitative research to be undertaken in groups of TB patients to directly consider the relative importance of different treatment outcomes, taking into consideration different sites of disease and drug susceptibility. The review findings may prove a useful resource in such work, to provide context or background for patients or perhaps to stimulate discussion.

Conclusions

This research presents a comprehensive synthesis of qualitative research of patient perspectives on TB and its treatment, ultimately producing a new theory about what constitutes patient important outcomes and why. The outcomes identified – improvement in the signs and symptoms of disease; mortality and survival; treatment failure, success and cure; the adverse effects of treatment; and the impact of treatment on the patient's ability to function and flourish in social, physical, developmental, educational or economic terms – should be considered within the development of a core outcome set for TB, but also by those planning future trials into the effectiveness of antituberculosis treatments and future qualitative research into outcome prioritisation for TB trials.

The research has provided a tentative rationale for the use of qualitative systematic reviews more widely within COS development. These methods have the potential to increase the volume, depth and diversity of the perspectives considered within the development of a COS, as well as identify the need for new research to be undertaken. However, these benefits should be considered in light of a trade-off against the significant time and resource required in conducting a qualitative systematic review, as well as the risk of over-interpreting evidence. More extensive use of these methods should perhaps wait until there is a greater volume of directly relevant qualitative research available. See Figure 9 for a full summary of the implications of this work for further research, practice and policy.

Figure 9. Implications of the findings for further research, practice and policy

- The following outcomes should be considered within the development of a core outcome set for TB, in future qualitative research into outcome prioritisation for TB trials, and in the planning of future trials of antituberculosis treatment:
  - improvement in the signs and symptoms of disease;
  - mortality and survival;
  - treatment failure, success and cure;
  - the adverse effects of treatment; and
  - the impact of treatment on the patient's ability to function and flourish in social, physical, developmental, educational or economic terms.
- There is a need for primary qualitative research to be conducted in patients in order to inform the development of a core outcome set for TB. Focus groups and interviews with TB patients should be undertaken to explicitly investigate their views on the relative importance of different treatment outcomes.
- Qualitative evidence synthesis methods have the potential to increase the volume, depth and diversity of the perspectives considered within the development of a core outcome set. However, these potential benefits should be considered in a trade-off against the considerable time and resources required in conducting a qualitative systematic review.
- The process of comparing existing clinical trials to the findings of a qualitative evidence synthesis of patient perspectives on treatment outcome prioritisation provides a useful tool for highlighting gaps in an existing evidence base. These gaps represent an absence of information of potential value to patients that should be investigated by future clincial trials.
- CERQual provides an effective, well-structured framework for assessing the extent to which the findings of a review are reasonable representation of the phenomena of interest. The CERQual framework should be incorporated into future qualitative evidence syntheses.

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Tugwell, P., Boers, M., Brooks, P., Simon, L., Strand, V. and Idzerda, L. (2007) 'OMERACT: An international initiative to improve outcome measurement in rheumatology', *Trials*, 8, pp. 38

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Williamson, P.R., Altman, D.G., Blazeby, J.M., Clarke, M., Devane, D., Gargon, E. and Tugwell, P. (2012a) 'Developing core outcome sets for clinical trials: issues to consider', *Trials*, 13, pp. 132

Williamson, P.R., Altman, D.G., Blazeby, J.M., Clarke, M. and Gargon, E. (2012b) 'Driving up the quality and relevance of research through the use of agreed core outcomes', *Journal of Health Services Research and Policy*, 17 (1), pp. 1-2

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Wolfe, F., Lassere, M., van der Heijde, D., Stucki, G., Suarez-Almazor, M., Pincus, T., Eberhardt, K., Kvein, T.K., Symmons, D., Silman, A., van Riel, P., Tugwell, P. and Boers, M. (1999) 'Preliminary Core Set of Domains and Reporting Requirements for Longitudinal Observational Studies in Rheumatology', *Journal of Rheumatology*, 26 (2), pp. 484-9

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World Health Organisation (2013) *Global tuberculosis report 2013.* Geneva: World Health Organisation

World Health Organisation (2013b) *Definitions and reporting framework for tuberculosis – 2013 revision.* Geneva: World Health Organisation

World Health Organisation (2015) *Global tuberculosis report 2015.* Geneva: World Health Organisation

Xu, B., Fochsen, G., Xiu, Y., Thorson, A., Kemp, J.R. and Jiang, Q.W. (2004) 'Perceptions and experiences of health care seeking and access to TB care – a qualitative study in Rural Jiangsu Province, China', *Health Policy*, 69, pp. 139–49

Xu, W., Lu, W., Zhou, Y., Zhu, L., Shen, H. and Wang, J. (2009) 'Adherence to anti-tuberculosis treatment among pulmonary tuberculosis patients: a qualitative and quantitative study', *BMC Health Services Research*, 9, pp. 169

Zhang, T., Liu, X., Bromley, H. and Tang, S. (2007) 'Perceptions of tuberculosis and health seeking behaviours in rural inner Mongolia, China', *Health Policy*, 81, pp. 155–65

Zhang, S.R., Yan, H., Zhang, J.J., Zhang, T.H., Li, X.H. and Zhang, Y.P. (2010) 'The experience of college students with pulmonary tuberculosis in Shaanxi, China: a qualitative study', *BMC Infectious Diseases*, 10, pp. 174

Zhang, Y., Du, L. and Fan, H. (no date) *Core outcome sets for tuberculosis*. COMET Initiative [online]. Available at: http://www.comet-initiative.org/studies/details/690?result=true (accessed: 10 September 2015)

Ziganshina, L.E., Titarenko, A.F. and Davies, G.R. (2013) 'Fluoroquinolones for treating tuberculosis (presumed drug-sensitive)', *Cochrane Database of Systematic Reviews*, 6, CD004795

Zuñiga, J.A., Muñoz, S.E., Johnson, M.Z. and Garcia, A. (2014) 'Tuberculosis Treatment for Mexican Americans Living on the U.S.-Mexico Border', *Journal of Nursing Scholarship*, 46 (4), pp. 253-62

Appendix A

Excluded studies list:

studies excluded after review at full paper-level

QUALITATIVE SYSTEMATIC REVIEW OF PATIENT PERSPECTIVES ON TUERCULOSIS AND ITS MANAGEMENT (ASSIA, CINAHL, EMBASE, MEDLINE, PSYCINFO)

note: duplicates have been removed

Paper	***Reason for exclusion***
Agho, K.E., Hall, J. and Ewald, B. (2014) 'Determinants of the Knowledge of and Attitude towards Tuberculosis in Nigeria', *Journal of Health, Population, and Nutrition*, 32 (3), pp. 520	Wrong study design
Armijos, R.X., Weigel, M.M., Qincha, M. and Ulloa, B. (2008) 'The meaning and consequences of tuberculosis for an at-risk urban group in Ecuador', *Revista Panamericana de Salud Publica/Pan American Journal of Public Health*, 23 (3), pp. 188-97	Wrong study design
Atkins, S., Biles, D., Lewin, S., Ringsberg, K. and Thorson, A. (2010) 'Patients' experiences of an intervention to support tuberculosis treatment adherence in South Africa', *Journal of Health Services Research & Policy*, 15 (3), pp. 163-70	No relevant information
Atkins, S., Launiala, A., Kagaha, A. and Smith, H. (2012) 'Including mixed methods research in systematic reviews: examples from qualitative syntheses in TB and malaria control', *BMC Medical Research Methodology*, 12, pp. 62	No relevant information
Atre, S., Kudale, A., Morankar, S., Gosoniu, D. and Weiss, M.G. (2011) 'Gender and community views of stigma and tuberculosis in rural Maharashtra, India', *Global Public Health*, 6 (1), pp. 56-71	Wrong population (not TB patients)

Ayisi, J.G., Van't Hoog, A.H., Agaya, J.A., Mchembere, W., Nyamthimba, P.O., Muhenje, O. and Marston B.J. (2011) 'Care seeking and attitudes towards treatment compliance by newly enrolled tuberculosis patients in the district treatment programme in rural western Kenya: a qualitative study', *BMC public health*, 11, pp. 515	No relevant information
Balgude, A. and Sontakke, S. 'Study of impact of antitubercular therapy on quality of life', *Indian Journal of Medical Sciences*, 66 (3-4), pp. 71-7	No relevant information
Baral, S.C., Karki, D.K. and Newell J.N. (2007) 'Causes of stigma and discrimination associated with tuberculosis in Nepal: A qualitative study', *BMC Public Health*, 7, art. 211	No relevant information
Bender, A., Peter, E., Wynn, F., Andrews, G. and Pringle, D. (2011) 'Welcome intrusions: An interpretive phenomenological study of TB nurses' relational work', *International Journal of Nursing Studies*, 48 (11), pp. 1409-19	Unable to locate
Boffa, J., King, M., McMullin, K. and Long, R. (2011) 'A process for the inclusion of Aboriginal people in health research: Lessons from the Determinants of TB Transmission project', *Social Science & Medicine*, 72 (5), pp. 733-8	No relevant information
Chileshe, M. and Bond, V.A. (2010) 'Barriers and outcomes: TB patients co-infected with HIV accessing antiretroviral therapy in rural Zambia', *AIDS Care*, 22 (Suppl. 1), pp. 51-9	Wrong population (HIV coinfection)
Chimbindi, N., Bärnighausen, T. and Newell, M-L. (2014) 'Patient satisfaction with HIV and TB treatment in a public programme in rural KwaZulu-Natal: evidence from patient-exit interviews', *BMC Health Services Research*, 14 (1), pp. 32	Wrong study design
Coreil, J., Mayard, G., Simpson, K.M., Lauzardo, M., Zhu, Y. and Weiss, M. (2010) 'Structural forces and the production of TB-related stigma among Haitians in two contexts', *Social Science & Medicine*, 71 (8), pp. 1409-17	No relevant information
Daftary, A. and Padayatchi, N. (2012) 'Social constraints to TB/HIV healthcare: Accounts from coinfected patients in South Africa', *AIDS Care*, 24 (12), pp. 1480-6	Wrong population (HIV coinfection)
Daftary, A., Padayatchi, N. and O'Donnell, M. (2014) 'Preferential adherence to antiretroviral therapy over tuberculosis treatment: A qualitative study of drug-resistant TB/HIV co-infected patients in South Africa', *Global Public Health*, 9 (9), pp. 1107-16	Wrong population (HIV coinfection)
Deribew, A., Tesfaye, M., Hailmichael, Y., Negussu, N., Daba, S., Wogi, A., Belachew, T., Apers, L. and Colebunders, R. (2009) 'Tuberculosis and HIV co-infection: Its impact on quality of life', *Health and Quality of Life Outcomes*, 7, art. 105	Wrong study design
Dodor, E.A. and Kelly, S. (2009) 'Health professionals as stigmatisers of tuberculosis: insights from community members and patients with TB in an urban district in Ghana', *Psychology, Health & Medicine*, 14 (3), pp. 301-10	No relevant information

Dodor, E.A. and Kelly, S. (2009) ‘"We are afraid of them': Attitudes and behaviours of community members towards tuberculosis in Ghana and implications for TB control efforts’, *Psychology, Health & Medicine*, 14 (2), pp. 170-179	Wrong population (not TB patients)
Dos Santos Lafaiete, R., da Motta, M.C.S. and Scatena Villa, T.C. (2011) ‘User satisfaction in the tuberculosis control program in a city in Rio de Janeiro, Brazil’, *Revista Latino-Americana de Enfermagem*, 19 (3), pp. 508-14	Wrong design
Gebremariam, M.K., Bjune, G.A. and Frich, J.C. (2010) ‘Barriers and facilitators of adherence to TB treatment in patients on concomitant TB and HIV treatment: a qualitative study’, *BMC Public Health*, 10, pp. 651	Wrong population (HIV coinfection)
Gebrekristos, H.T., Lurie, M.N., Mthethwa, N. and Karim, Q.A. (2009) ‘Disclosure of HIV status: experiences of patients enrolled in an integrated TB and HAART pilot programme in South Africa... highly active antiretroviral therapy’, *African Journal of AIDS Research*, 8 (1), pp. 1-6	Wrong population (HIV coinfection)
Gibson, N., Cave, A., Doering, D., Gibson, N., Harms, P. and Ortiz, L. (2005) ‘Socio-cultural factors influencing prevention and treatment of tuberculosis in immigrant and Aboriginal communities in Canada’, *Social Science & Medicine*, 61 (5), pp. 931-942	No relevant information
Haasnoot, P.J., Boeting, T.E., Kuney, M.O. and Van Roosmalen, J. (2010) ‘Knowledge, attitudes, and practice of tuberculosis among Maasai in Simanjiro District, Tanzania’, *American Journal of Tropical Medicine and Hygiene*, 83 (4), pp 902-5	No relevant information
Hernandez Sarmiento, J.M., Davila Osorio, V.L., Martinez Sanchez, L.M., Restrepo Serna, L., Grajales Ospina, D.C., Toro Montoya, A.E., Arango Urrea, V., Vargas Grisales, N., Estrada Gomez, M., Lopera Valle, J.S., Garcia Gil, J.J., Restrepo, L., Mejia, G., Zapata, E., Gomez, V., Lopera, D., Domico Domico, J.L. and Robledo, J. (2013) ‘Tuberculosis in indigenous communities of Antioquia, Colombia: Epidemiology and beliefs’, *Journal of Immigrant and Minority Health*, 15 (1), pp. 10-6	No relevant information
Heunis, J.C., Van Rensburg, H.C.J. and Muelemans, H. (2007) ‘SANTA vs. public tuberculosis hospitals: the patient experience in the Free State, 2001/2002’, *Curationis*, 30 (1), pp. 4-14	Wrong study design
Horwitz, L.D. and Horwitz, M. (2014) ‘The exochelins of pathogenic mycobacteria: unique, highly potent, lipid- and water-soluble hexadentate iron chelators with multiple potential therapeutic uses’, Antioxidants & redox signalling, 21 (16), 2246-61	Wrong study design
Hu, A., Loo, E., Winch, P.J. and Surkan, P.J. (2012) ‘Filipino Women's Tuberculosis Care Seeking Experience in an Urban Poor Setting: A Socioecological Perspective’, *Health Care for Women International*, 33 (1), pp. 29-44	No relevant information
Huffman, S.A., Veen, J., Hennink, M.M. and McFarland, D.A. (2012) ‘Exploitation, vulnerability to tuberculosis and access to treatment among Uzbek labor migrants in Kazakhstan’, *Social Science & Medicine*, 74 (6), pp. 864-72	Wrong population (not TB patients)

Isaakidis, P., Rangan, S., Pradhan, A., Ladomirska, J., Reid, T. and Kielmann, K. (2013) 'I cry every day': experiences of patients co-infected with HIV and multidrug-resistant tuberculosis', *Tropical Medicine & International Health*, 18 (9), pp. 1128-33	Wrong population (HIV coinfection)
Janakan, N. and Seneviratne, R. (2008) 'Factors contributing to medication noncompliance of newly diagnosed smear-positive pulmonary tuberculosis patients in the District of Colombo, Sri Lanka', *Asia-Pacific Journal of Public Health*, 20 (3), pp. 214-23	Wrong study design
Johansson, E. and Winkvist, A. (2002) 'Trust and Transparency in Human Encounters in Tuberculosis Control: Lessons Learned from Vietnam', *Qualitative Health Research*, 12 (4), pp. 473-91	Published before 2003
Joseph, H.A., Waldman, K., Rawls, C., Wilce, M. and Shrestha-Kuwahara, R. (2008) 'TB Perspectives among a Sample of Mexicans in the United States: Results from an Ethnographic Study', *Journal of Immigrant and Minority Health*, 10 (2), pp. 177-185	Wrong population (not TB patients)
Kaona, F.A.D., Tuba, M., Siziya, S. and Sikaona L. (2004) 'An assessment of factors contributing to treatment adherence and knowledge of TB transmission among patients on TB treatment', *BMC Public Health*, 4, art. 68	No relevant information
Karim, F., Chowdhury, A.M.R., Islam, A. and Weiss, M.G. (2007) 'Stigma, gender, and their impact on patients with tuberculosis in rural Bangladesh', *Anthropology & Medicine*, 14 (2), pp. 139-51	No relevant information
Karim, F., Johansson, E., Diwan, V.K. and Kulane, A. (2011) 'Community perceptions of tuberculosis: A qualitative exploration from a gender perspective', *Public Health*, 125 (2), pp. 84-9	Wrong population (not TB patients)
Khan, M.A., Walley, J.D., Witter, S.N., Shah, S.K. and Javeed, S. (2005) 'Tuberculosis patient adherence to direct observation: Results of a social study in Pakistan', *Health Policy and Planning*, 20 (6), pp. 354-65	No relevant information
Kirwan, D.E., Nicholson, B.D., Baral, S.C. and Newell, J.N. (2009) 'The social reality of migrant men with tuberculosis in Kathmandu: implications for DOT in practice', *Tropical Medicine & International Health*, 14 (12), pp. 1442-7	No relevant information
Koch, E. (2013) 'Tuberculosis is a threshold: The making of a social disease in post-Soviet Georgia', *Medical Anthropology*, 32 (4), pp. 309-24	No relevant information
Kulane, A., Ahlberg, B.M. and Berggren, I. (2010) '"It is more than the issue of taking tablets": The interplay between migration policies and TB control in Sweden', *Health Policy*, 97 (1), pp. 26-31	No relevant information
Legesse, M., Ameni, G., Mamo, G., Medhin, G., Bjune, G. and Abebe, F. (2011) 'Knowledge of cervical tuberculosis lymphadenitis and its treatment in pastoral communities of the Afar region, Ethiopia', *BMC Public Health*, 11, pp. 157	Wrong study design

Lewis, C.P. and Newell, J.N. (2009) 'Improving tuberculosis care in low income countries - A qualitative study of patients' understanding of "patient support" in Nepal', *BMC Public Health*, 9, art. 190	No relevant information
Macdonald, M.E., Rigillo, N. and Brassard, P. (2010) 'Urban Aboriginal understandings and experiences of tuberculosis in Montreal, Quebec, Canada', *Qualitative Health Research*, 20 (4), pp. 506-23	No relevant information
Mahendradhata, Y., Ahmad, R.A., Lefèvre, P., Boelaert, M. and Stuyft, P.V. (2008) 'Barriers for introducing HIV testing among tuberculosis patients in Jogjakarta, Indonesia: a qualitative study', *BMC Public Health*, 8, pp. 385	No relevant information
Marra, C.A., Marra, F., Cox, V.C., Palepu, A. and Fitzgerald, J.M. (2004) 'Factors influencing quality of life in patients with active tuberculosis', *Health and Quality of Life Outcomes*, 2, art. 58	No relevant information
Mauch, V., Melgen, R., Marcelino, B., Acosta, I., Klinkenberg, E. and Suarez, P. (2013) 'Tuberculosis patients in the Dominican Republic face severe direct and indirect costs and need social protection', *Revista Panamericana de Salud Publica*, 33 (5), pp. 332-9	Wrong study design
Mauch, V., Woods, N., Kirubi, B., Kipruto, H., Sitienei, J. and Klinkenberg, E. (2011), 'Assessing access barriers to tuberculosis care with the tool to Estimate Patients' Costs: pilot results from two districts in Kenya', *BMC public health*, 11, pp. 43	Wrong study design
Mesfin, M.M., Newell, J.N., Walley, J.D., Gessessew, A., Tesfaye, T., Lemma F. and Madeley, R.J. (2009) 'Quality of tuberculosis care and its association with patient adherence to treatment in eight Ethiopian districts', *Health Policy & Planning*, 24 (6), pp. 457-66	Wrong study design
Metcalf, E.P., Davies, J.C., Wood, F. and Butler, C.C. (2007) 'Unwrapping the diagnosis of tuberculosis in primary care: A qualitive study', *British Journal of General Practice*, 57 (535), pp. 116-22	No relevant information
Moffatt, J., Mayan, M. and Long, R. (2013) 'Sanitoriums and the Canadian colonial legacy: The untold experiences of tuberculosis treatment', Qualitative Health Research, 23 (12), pp. 1591-9	No relevant information
Mohammed, S., Siddiqi, O., Ali, O., Habib, A., Haqqi, F., Kausar, M. and Khan, A.J. (2012) 'User engagement with and attitudes towards an interactive SMS reminder system for patients with tuberculosis', *Journal of Telemedicine and Telecare*, 18 (7), pp. 404-8	Unable to locate
Murray, E.J., Bond, V.A., Marais, B.J., Godfrey-Faussett, P., Ayles, H.M. and Beyers, N. (2013) 'High levels of vulnerability and anticipated stigma reduce the impetus for tuberculosis diagnosis in Cape Town, South Africa', *Health Policy and Planning*, 28 (4), pp. 410-8	Wrong population (large HIV burden; not all patients – not sufficient information to disentangle)

Muture, B.N., Keraka, M.N., Kimuu, P.K., Kabiru, E.W., Ombeka, V.O. and Oguya, F. (2011) 'Factors associated with default from treatment among tuberculosis patients in Nairobi province, Kenya: a case control study', *BMC Public Health*, 11, pp. 696	Wrong study design
Naidoo, P. and Mwaba, K. (2010) 'Helplessness, depression, and social support among people being treated for tuberculosis in South Africa', *Social Behavior and Personality*, 38 (10), pp. 1323-34	No relevant information
Ngamvithayapong-Yanai, J., Winkvist, A., Luangjina, S. and Diwan, V. (2005) '"If we have to die, we just die": challenges and opportunities for tuberculosis and HIV/AIDS prevention and care in northern Thailand', *Qualitative Health Research*, 15 (9), pp. 1164-79	No relevant information
Noyes, J. and Popay, J. (2007) 'Directly observed therapy and tuberculosis: how can a systematic review of qualitative research contribute to improving services? A qualitative meta-synthesis', *Journal of Advanced Nursing*, 57 (3), pp. 227-43	No relevant information
Peltzer, K., Naidoo, P., Matseke, G., Louw, J., Mchunu, G. and Tutshana, B. (2012) 'Prevalence of psychological distress and associated factors in tuberculosis patients in public primary care clinics in South Africa', *BMC Psychiatry*, 12, art. 89	Wrong study design
Pinto, L.M. and Udwadia, Z.F. (2010) 'Private patient perceptions about a public programme; what do private Indian tuberculosis patients really feel about directly observed treatment?', *BMC public health*, 10, pp. 357	No relevant information
Rintiswati, N., Mahendradhata, Y., Suharna, S., Purwanta, S.Y., Varkevisser, C.M. and Van Der Werf, M.J. (2009) 'Journeys to tuberculosis treatment: A qualitative study of patients, families and communities in Jogjakarta, Indonesia', *BMC Public Health*, 9, art. 158	No relevant information
Shiotani, R. and Hennink, M. (2014) 'Socio-cultural influences on adherence to tuberculosis treatment in rural India', *Global Public Health*, 9 (10), 1239-51	No relevant information
Sagbakken, M., Bjune, G.A. and Frich, J.C. (2012) 'Humiliation or care? A qualitative study of patients' and health professionals' experiences with tuberculosis treatment in Norway', *Scandinavian Journal of Caring Sciences*, 26 (12), pp. 313-23	No relevant information
Sagbakken, M., Frich, J.C. and Bjune, G.A. (2008) 'Perception and management of tuberculosis symptoms in Addis Ababa, Ethiopia', *Qualitative Health Research*, 18 (10), pp. 1356-66	No relevant information
Seyoum, A. and Legesse, M. (2013) 'Knowledge of tuberculosis (TB) and human immunodeficiency virus (HIV) and perception about provider initiated HIV testing and counselling among TB patients attending health facilities in Harar town, Eastern Ethiopia', *BMC public health*, 13, pp. 124	Wrong study design

Sharma, N., Nath, A., Taneja, D.K. and Ingle, G.K. (2009) 'A qualitative evaluation of the information, education, and communication component of the tuberculosis control program in Delhi, India', *Asia-Pacific Journal of Public Health*, 21 (3), pp. 321-32	No relevant information
Shiotani, R. and Hennink, M. (2014) 'Socio-cultural influences on adherence to tuberculosis treatment in rural India', *Global Public Health*, 9 (10), pp. 1239-51	No relevant information
Terra, M.F. and Bertolozzi, M.R. (2008) 'Does directly observed treatment ("DOTS") contribute to tuberculosis treatment compliance?', *Revista Latino-Americana de Enfermagem*, 16 (4), pp. 659-64	Wrong population (not TB patients)
Van Rie, A., Sengupta, S., Pungrassami, P., Balthip, Q., Choonuan, S., Kasetjaroen, Y., Strauss, R.P. and Chongsuvivatwong, V. (2008) 'Measuring stigma associated with tuberculosis and HIV/AIDS in southern Thailand: exploratory and confirmatory factor analyses of two new scales', *Tropical Medicine & International Health*, 13 (1), pp. 21-30	Wrong study design
Van Schalkwyk, G., De Vries, J. and Moodley, K. (2012) '"It's for a good cause, isn't it?" - Exploring views of South African TB research participants on sample storage and re-use', *BMC Medical Ethics*, 13, art. 19	No relevant information
Verhagen, L., Kapinga, R. and Rosmalen-Nooijens, K. (2010) 'Factors underlying diagnostic delay in tuberculosis patients in a rural area in Tanzania: a qualitative approach', *Infection*, 38 (6), pp. 433-46	No relevant information
Vukovic, D.S. and Nagorni-Obradovic, L.M. (2011) 'Knowledge and awareness of tuberculosis among Roma population in Belgrade: A qualitative study', *BMC Infectious Diseases*, 11, art. 284	No relevant information
Wade, V.A., Karnon, J., Eliott, J.A. and Hiller, J.E. (2012) 'Home videophones improve direct observation in tuberculosis treatment: a mixed methods evaluation', *PLoS ONE*, 7 (11), art. e50155	No relevant information
Wandwalo, E., Makundi, E., Hasler, T. and Morkve, O. (2006) 'Acceptability of community and health facility-based directly observed treatment of tuberculosis in Tanzanian urban setting', *Health Policy*, 78 (2-3), pp. 284-94	No relevant information
Watkins, R.E. and Plant, A.J. (2004) 'Pathways to treatment for tuberculosis in Bali: patient perspectives', *Qualitative Health Research*, 14 (5), pp. 691-703	No relevant information
Wei, X., Chen, J., Chen, P., Newell, J.N., Li, H., Sun, C., Mei, J. and Walley, J.D. (2009) 'Barriers to TB care for rural-to-urban migrant TB patients in Shanghai: a qualitative study', *Tropical Medicine & International Health*, 14 (7), pp. 754-60	No relevant information
West, E.L., Gadkowski, L.B., Ostbye, T., Piedrahita, C. and Stout J.E. (2008) 'Tuberculosis knowledge, attitudes, and beliefs among North Carolinians at increased risk of infection', *North Carolina medical journal*, 69 (1), pp. 14-20	Wrong population (not TB patients)

Wieland, M.L., Weis, J.A., Yawn, B.P., Sullivan, S.M., Millington, K.L., *et al.* (2012) 'Perceptions of Tuberculosis Among Immigrants and Refugees at an Adult Education Center: A Community-Based Participatory Research Approach', *Journal of Immigrant and Minority Health*, 14 (1), pp. 14-22	Wrong population (not TB patients)
Wynne, A., Richter, S., Jhangri, G.S., Alibhai, A., Rubaale, T. and Kipp, W. (2014) 'Tuberculosis and human immunodeficiency virus: exploring stigma in a community in western Uganda', *AIDS Care*, 69 (2), pp. 940-6	Wrong population (not all TB patients, some HIV)
Xu, B., Fochsen, G., Xiu, Y., Thorson, A., Kemp, J.R. and Jiang, Q.W. (2004) 'Perceptions and experiences of health care seeking and access to TB care -- a qualitative study in Rural Jiangsu Province, China', *Health Policy*, 69 (2), pp. 139-49	No relevant information
Yin, X., Tu, X., Tong, Y., Yang, R., Wang, Y., Cao, S., Fan, H., Wang, F., Gong, Y., Yin, P. and Lu, Z. (2012) 'Development and validation of a Tuberculosis Medication Adherence Scale', *PLoS ONE*, 7 (12), art. e50328	Wrong study design
Zolowere, D., Manda, K., Panulo, B. and Muula, A.S. (2008) 'Experiences of self-disclosure among tuberculosis patients in rural Southern Malawi', *Rural & Remote Health*, 8 (4), pp. 1037	No relevant information
Zvavamwe, Z. and Ehlers, V.J. (2009) 'Experiences of a community-based tuberculosis treatment programme in Namibia: A comparative cohort study', *International Journal of Nursing Studies*, 46 (3), pp. 302-9	No relevant information

COCHRANE INTERVENTION REVIEWS OF TUBERCULOSIS TREATMENT (COCHRANE DATABASE OF SYSTEMATIC REVIEWS)

Paper	***Reason for exclusion***
Mayosi, B.M., Ntsekhe, M., Volmink, J.A. and Commerford, P.J. (2002) 'Interventions for treating tuberculous pericarditis', *Cochrane Database of Systematic Reviews*, 4, CD000526	Wrong intervention (not antituberculosis chemotherapy)
Fraser, A., Paul, M., Attamna, A. and Leibovici, L. (2006) 'Drugs for preventing tuberculosis in people at risk of multiple-drug-resistant pulmonary tuberculosis', *Cochrane Database of Systematic Reviews*, 2, CD005435	Wrong population (latent infection)

QUALITATIVE OUTCOMES RESEARCH IN PATIENTS (COMET INITIATIVE REGISTER)

Paper	***Reason for exclusion***
Blazeby, J.M., Macefield, R., Blencowe, N.S., Jacobs, M., McNair, A.G., Sprangers, M., Brookes, S.T. on behalf of the Research, Consensus Groups of the Core, Outcomes iNformation, SEts iN SUrgical Studies Oesophageal Cancer group (2015) 'Core information set for oesophageal cancer surgery', *British Journal of Surgery*, 102(8), pp. 936-43	Wrong design (quantitative/thin data)
Chalmers, J. R., Schmitt, J., Apfelbacher, C., Dohil, M., Eichenfield, L.F., Simpson, E.L., Singh, J., Spuls, P., Thomas, K., Admani, S., Aoki, V., Ardeleanu, M., Barbarot, S., Berger, T., Bergman, J.N., Block, J., Borok, N., Burton, T., Chamlin, S.L., Deckert, S., DeKlotz, C.C., Graff, L.B., Hanifin, J.M., Hebert, A.A., Humphreys, R., Katoh, N., Kisa, R.M., Margolis, D.J., Merhand, S., Minnillo, R., Mizutani, H., Nankervis, H., Ohya, Y., Rodgers, P., Schram, M.E. Stalder, J.F., Takaoka, R., Svensson, A., Teper, A., Tom, W.L., Von Kobyletzki, L., Weisshaar, E., Zelt, S. and Williams, H.C. (2014) 'Report from the Third International Consensus Meeting to Harmonise Core Outcome Measures for Atopic Eczema / Dermatitis Clinical Trials (HOME)', *British Journal of Dermatology*, 1 (10), pp. 13237	Wrong design (quantitative/thin data)
Chitnis, T., Tenembaum, S., Banwell, B., Krupp, L., Pohl, D., Rostasy, K., Yeh, E.A., Bykova, O., Wassmer, E., Tardieu, M., Kornberg, A. and Ghezzi, A. (2012) 'Consensus statement: evaluation of new and existing therapeutics for pediatric multiple sclerosis', *Multiple Sclerosis*, 18 (1), pp. 116-27	Wrong design (quantitative/thin data)
Coulman, K.D., Owen-Smith, A., Andrews, R.C., Chalmers, K., Ferguson, Y., Norton, S., Welbourn, R., Whale, K. and Blazeby, J.M. (2014) 'The patient perspective of bariatric surgery outcomes: Developing a 'core' set of patient-reported outcomes', *Obesity Surgery*, 24 (8), pp. 1296	Wrong design (quantitative/thin data)
Eleftheriadou, V., Thomas, K., *et al*. on behalf of the Vitiligo Global Issues Consensus Group (VGICG) (2015) 'Developing core outcome set for vitiligo clinical trials: international e-Delphi consensus', *Pigment Cell and Melanoma Research*, 28 (3), pp. 363-9	Wrong design (quantitative/thin data)
Eleftheriadou, V., Thomas, K., Whitton, M.E., Batchelor, J.M. and Ravenscroft, J.C. (2012) 'Which outcomes should we measure in vitiligo? Results of a systematic review and a survey amongst patients and clinicians on outcomes in vitiligo trials', *British Journal of Dermatology*, 167 (4), pp. 804-14	Wrong design (quantitative/thin data)
Feldman, L.S., Lee, L. and Fiore, J. (2015) 'What outcomes are important in the assessment of Enhanced Recovery After Surgery (ERAS) pathways?', Canadian Journal of Anaesthesia, 62 (2), pp. 120-30	Wrong design (narrative review)
Fitzpatrick, R., Chambers, J., Burns, T., Doll, H., Fazel, S., Jenkinson, C., Kaur, A., Knapp, M., Sutton, L. and Yiend, J. (2010) 'A systematic review of outcome measures used in forensic mental health research with consensus panel opinion', *Health Technology Assessment*, 14 (8)	Wrong design (quantitative/thin data)

Gladman, D.D., Mease, P.J., Strand, V., Healy, P., Helliwell, P.S., Fitzgerald, O., Gottlieb, A.B., Krueger, G.G., Nash, P., Ritchlin, C.T. Taylor, W., Adebajo, A., Braun, J., Cauli, A., Carneiro, S., Choy, E., Dijkmans, B., Espinoza, L., Van der Heijde, D., Husni, E., Lubrano, E., McGonagle, D., Qureshi, A., Soriano, E.R. and Zochling, J. (2007) 'Consensus on a core set of domains for psoriatic arthritis', *Journal of Rheumatology*, 34 (5), pp. 1167-70	Wrong design (quantitative/thin data)
Gladman, D.D. (2005) 'Consensus exercise on domains in psoriatic arthritis', *Annals of the Rheumatic Diseases*, 64 (Suppl 2), pp. ii113-4	Wrong design (quantitative/thin data)
Hammarlund, S., Nilsson, C. and Hagell, P.M.H. (2012) 'Measuring outcomes in Parkinson's disease: a multi-perspective concept mapping study', *Quality of Life Research*, 21 (3), pp. 453-63	Wrong design (quantitative/thin data)
Mease, P.J., Arnold, L.M., Crofford, L.J., Williams, D.A., Russell, I.J., Humphrey, L., Abetz, L. and Martin, S.A. (2008) 'Identifying the clinical domains of fibromyalgia: contributions from clinician and patient Delphi exercises', *Arthritis Rheum*, 59 (7), pp. 952-60	Wrong design (quantitative/thin data)
Mease, P.A., Choy, L.M., Clauw, E.H., Crofford, D.J., Leslie J. Glass, Martin, J.M., Morea, S.A., Simon, J., Strand, L.C. Vibeke Williams, D.A. on behalf of the Omeract Fibromyalgia Working Group (2009) 'Fibromyalgia syndrome module at OMERACT 9: domain construct', *Journal of Rheumatology*, 36 (10), pp. 2318-29	Wrong design (quantitative/thin data)
Morris, C., Janssens, A., Allard, A., Thompson-Coon, J., Shilling, V., Tomlinson, R., Williams, J., Fellowes, A., Rogers, M., Allen, K., Beresford, B. and Green, C. (2014) 'Informing the NHS Outcomes Framework: evaluating meaningful health outcomes for children with neurodisability using multiple methods including systematic review, qualitative research, Delphi survey and consensus meeting', *Health Services and Delivery Research*, 2 (15)	Wrong design (quantitative/thin data)
Paul, L., Coote, S., Crosbie, J., Dixon, D., Hale, L., Holloway, E., McCrone, P., Miller, L., Saxton, J., Sincock, C. and White, L. (2014) 'Core outcome measures for exercise studies in people with multiple sclerosis: recommendations from a multidisciplinary consensus meeting', *Multiple Sclerosis*, 17, pp. 17	Wrong design (quantitative/thin data)
Salaffi, F., Ciapetti, A., Sarzi Puttini, P., Atzeni, F., Iannuccelli, C., Di Franco, M., Cazzola, M. and Bazzichi, L. (2012) 'Preliminary identification of key clinical domains for outcome evaluation in fibromyalgia using the Delphi method: The Italian experience', *Reumatismo*, 64 (1), pp. 27-34	Wrong design (quantitative/thin data)
Scher, H.I., Eisenberger, M., D'Amico, A.V., Halabi, S., Small, E.J., Morris, M., Kattan, M.W., Roach, M., Kantoff, P., Pienta, K.J., Carducci, MA., Agus, D., Slovin, S.F., Heller, G., Kelly, W.K., Lange, P.H., Petrylak, D., Berg, W., Higano, C., Wilding, G., Moul, J.W., Partin, A.N., Logothetis, C. and Soule, H.R. (2004) 'Eligibility and outcomes reporting guidelines for clinical trials for patients in the state of a rising prostate-specific antigen: recommendations from the Prostate-Specific Antigen Working Group', *Journal of Clinical Oncology*, 22 (3), pp. 537-56	Wrong design (quantitative/thin data)

Schmitt, J.L., Stamm, S., Williams, T., Hywel, C., on behalf of the Harmonizing Outcome Measurements in Eczema Delphi panel (2011) 'Core outcome domains for controlled trials and clinical recordkeeping in eczema: international multiperspective Delphi consensus process', *Journal of Investigative Dermatology*, 131 (3), 623-30	Wrong design (quantitative/thin data)
Singh, J.A., Taylor, W.J., Dalbeth, N., Simon, L.S., Sundy, J., Grainger, R., Alten, R., March, L., Strand, V., Wells, G., Khanna, D., McQueen, F., Schlesinger, N., Boonen, A., Boers, M., Saag, K.G., Schumacher, H.R. and Edwards, N.L. (2014) 'OMERACT endorsement of measures of outcome for studies of acute gout', *Journal of Rheumatology*, 41 (3), pp. 569-73	Wrong design (quantitative/thin data)
Sinha, I.P., Gallagher, R., Williamson, P.R. and Smyth, R.L. (2012) 'Development of a core outcome set for clinical trials in childhood asthma: a survey of clinicians, parents, and young people', *Trials*, 13, 103	Wrong design (quantitative/thin data)
Smelt, A.F., Louter, M.A., Kies, D.A., Blom, J.W., Terwindt, G.M., Van der Heijden, G.J,. De Gucht, V., Ferrari, M.D. and Assendelft, W.J. (2014) 'What do patients consider to be the most important outcomes for effectiveness studies on migraine treatment? Results of a Delphi study', *PLoS ONE*, 9 (6), pp. e98933	Wrong design (quantitative/thin data)
Turk, D.C., Dworkin, R.H., Revicki, D.H., Gale Burke, L.B. Cella, D.C., *et al*. (2008) 'Identifying important outcome domains for chronic pain clinical trials: an IMMPACT survey of people with pain', *Pain*, 137 (2), pp. 276-85	Wrong design (quantitative/thin data)
Urbach, D.R., Harnish, J.L. and Long, G. (2005) 'Short-term health-related quality of life after abdominal surgery: a conceptual framework', *Surgical Innovation*, 12 (3), 243-7	Wrong design (quantitative/thin data)
Wylde, V., MacKichan, F., Bruce, J. and Gooberman-Hill, R. (2014) 'Assessment of chronic post-surgical pain after knee replacement: Development of a core outcome set', *European Journal of Pain*, 19 (5), pp. 611-20	Wrong design (quantitative/thin data)