

Invited Commentary

A global, adaptive, platform trial to reduce death and disability from tuberculous meningitis

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Before the advent of anti-tuberculosis drugs in the 1940's, tuberculous meningitis (TBM) was a much feared and almost universally fatal form of tuberculosis. Thus when the first anti-tuberculosis drugs, streptomycin and para-aminosalicylic acid (PAS), became available, they were given first to those with TBM. Suddenly, the disease became treatable. Case-fatality fell from 70% with streptomycin and PAS, to around 30% with the combination of isoniazid, pyrazinamide and rifampicin[1].

Sadly, progress has slowed over the last 30 years. TBM case-fatality is stuck at around 25% in HIV negative individuals and up to 50% in those living with HIV, and nearly everyone dies or is left disabled if the disease is caused by multi-drug resistant *Mycobacterium tuberculosis*[2]. Interventions to improve these depressing figures fall into those which enhance bacterial killing, usually by optimising intracerebral anti-tuberculosis drug exposures, and those which control brain inflammation, which has long been recognised as a major contributor to TBM-related death and neurological disability.

Over the last two decades, a small number of randomised controlled trials have been conducted aiming at improving TBM outcomes[2]. The interventions tested include higher doses of rifampicin (15-35mg/kg)[3], adding anti-tuberculosis drugs with good brain penetration (e.g. fluoroquinolones, linezolid)[4], or controlling brain inflammation with adjunctive corticosteroids and aspirin[5]. However, with the exception of adjunctive corticosteroids which reduced death (but not disability) in HIV negative individuals with TBM[6], the trials of the last 20 years have not established new, outcome-improving, changes in treatment.

The lack of success might be explained by the relative rarity of TBM, the difficulties confirming the diagnosis, the challenges of enrolling very unwell patients into trials, and limited interest from funding agencies. But in general the trials conducted have been too small (<800 participants), too slow to recruit (often just one or two centres), and have only investigated one, sometimes two,

interventions at a time. Furthermore, there are currently three active trials investigating the same intervention (high dose rifampicin)[2], suggesting potential duplication of effort.

In contrast to the modest achievements of TBM research over the last two decades, the wider advances in treating pulmonary tuberculosis have been spectacular. A resurgent anti-tuberculosis drug pipeline and associated clinical trials have produced an entirely new, oral, highly effective 6-month treatment regimen (bedaquiline, pretomanid, linezolid) for multi-drug resistant pulmonary tuberculosis[7]; a regimen that shortens pulmonary tuberculosis treatment to 4 months[8]; and innovative phase 2 trials that will speed the passage of more new drugs into phase 3 trials and clinical practice[9]. There is also growing interest in novel adjunctive therapies that target specific components of tuberculosis inflammation linked to substantial long-term morbidity in survivors[10].

It is time for TBM research to catch up. The panoply of new and emerging antimicrobial and adjunctive anti-inflammatory agents offer an unparalleled opportunity to reduce TBM morbidity and mortality. But if we continue to conduct small trials, testing one intervention at a time, with an inflexible and poorly coordinated approach, our patients will be no better off in ten years' time. A new TBM clinical trials platform is needed which will enable the efficient testing of new drugs and regimens as they emerge from phase 2 trials, running in parallel with the trials conducted in pulmonary tuberculosis.

We therefore propose a global, phase 3, adaptive, multi-stage randomised controlled platform trial that will investigate multiple interventions to reduce death and disability from TBM, at scale and at speed. The trial platform will be built across Asia and Africa because this is where most of the disease and the expertise to tackle it resides. We will coordinate with the 'Tuberculous Meningitis International Research Consortium', a 15 year-old global community of TBM researchers, to which the authors belong, to ensure we include the world's leading TBM investigators and trial sites. The design and delivery of the trial, and the uptake of the results, will depend upon the strength of this global consortium, the trust between members and their substantial external influence.

The trial will be as pragmatic as possible, whilst not compromising on rigor and quality. The trial must have the capacity to investigate new anti-tuberculosis or anti-inflammatory drugs, therefore must be able to support submissions to regulatory agencies. The pragmatism, therefore, will come from broad inclusion criteria, reducing unnecessary barriers to participation thus ensuring real-world relevance of the results, and by the use of easily ascertained outcomes that matter to patients. We envisage a modular protocol, with a 'core' component for all sites that articulates the essential elements of the trial, with the optional addition of modules (e.g. pathophysiology, pharmacology) for the research intensive centres.

In the first stage of the platform's activities (years 1-4) there will be two main objectives. The first will be to identify one or more 26-week regimens either non-inferior or superior to the current WHO-recommended 52-week standard-of-care regimen, which would then become the new 'standard-of-care' in stage 2 of the platform. A stringent non-inferiority margin would be required (relative risk of at most 10% increased mortality or disability). At least one of these regimens should be rifampicin-free. A regimen for rifampicin-resistant TBM is urgently needed, and rifampicin has extensive drug-drug interactions, complicating co-administration and hindering the development of novel, highly active regimens containing new drugs. Bedaquiline-based regimens have fewer interactions than rifampicin-based regimens and are highly effective in treating multi-drug resistant tuberculosis, making them an attractive backbone for new TBM regimens. The second objective will be to determine whether enhanced early immunomodulation, with higher corticosteroid doses, aspirin, or TNF- α antagonists (e.g. infliximab), is superior to the current standard-of-care dexamethasone. In the second stage (years 5-10) the platform would substitute new anti-tuberculosis and anti-inflammatory drugs emerging from phase 2 trials into the new 'standard-of-care' regimens identified in stage 1, thereby seeking to further reduce death and disability from TBM. Decisions to replace the current standard of care would be based on showing superiority.

The interventions tested by the trial in stage 1 (including the drug choices and doses) needs discussion and agreement with the TBM consortium trial investigators, and industry collaborators where appropriate. Intervention choice may also be informed by animal models[11]. As in previous trials, the interventions will sub-divide into those which enhance bacterial killing, and those which control brain inflammation. Both can be hypothesised to reduce death and neurological disability from TBM, with the advantage that their limited or absent interaction enables a factorial trial design (figure 1).

The trial will enroll anyone with suspected TBM, regardless of HIV status. The trial may start in adults, but TBM is common in children, often with devastating outcomes, and extension into all age-groups should be a priority. We and others in the TBM consortium are investigators in the active, multi-centre (Asia and Africa), SURE trial in childhood TBM (ISRCTN40829906), representing an infrastructure for including children in the proposed trial. Intervention-specific exclusion criteria are inevitable, but will be kept to a minimum. The primary outcome will be death or disability, assessed monthly in person or by phone using the modified Rankin score, up to 52 weeks after randomisation[12]. Secondary outcomes will be limited to the common inflammatory intracerebral complications of treatment (so-called paradoxical reactions, or immune reconstitution inflammatory syndrome (IRIS) in those initiating anti-retroviral treatment), drug-related serious adverse events, treatment failure and relapse.

To enable the efficient selection of the regimens most likely to improve upon the current standard-of-care we will use a multi-arm multi-stage adaptive design. An independent data monitoring committee will make regular pre-specified comparisons of death and disability and drug-related adverse events in the intervention arms relative to the standard of care. Poorly performing interventions can be dropped for futility. The arms predicted most likely to improve upon standard-of-care will continue to enroll. The majority (>80%) of deaths in TBM occur within 2 months of treatment initiation, allowing for rapid ascertainment of most endpoints. This allows for regular

interim analyses using patient data right censored at the most recent follow-up. Improvements on current standard-of-care would most likely be moderate (~20% reduction in death or disability). In stage 1, showing non-inferiority or superiority of a marginally better regimen (10% reduction in mortality or more) would require around 500 patients per intervention under a non-inferiority margin of 4 percentage points. With the engagement of the TBM consortium trials community, we anticipate recruiting at least 500 participants each year.

Intra-cerebral inflammatory reactions occur in around 20% of patients, usually 4-12 weeks after starting TBM treatment. They include the expansion of space-occupying lesions (tuberculomas) and vasculitis with multiple infarcts. Around 30% of these reactions result in death or disability, but their management has never been subject to randomised controlled trials. Generally, corticosteroids are given (e.g. dexamethasone), but the optimal dose and duration is unknown[13]. Targeted anti-inflammatory drugs are hypothesised to be safer and more effective than corticosteroids, but support for their use is limited to case-series. These drugs include antagonists of the cytokines TNF- α (e.g. infliximab, thalidomide) and IL-1 β (e.g. anakinra)[14, 15].

Given the on-going uncertainty surrounding the management of the inflammatory reactions and the lack of relevant trial data, trial participants suffering these events (defined clinically and radiologically) will be eligible for a third randomisation (**figure 1**). We will likely compare two interventions initially – high dose corticosteroids and infliximab – with the primary outcome being death or disability 12 months from the baseline randomisation. As around 20% of trial participants will be eligible, and the anticipated effect sizes on the primary outcome are unknown, this part of the trial would be exploratory. We will take advantage of the platform design to continue randomisation into stage 2, until such time as the data monitoring committee recommend stopping based on efficacy, safety, or futility.

In summary, we propose a global, adaptive, multi-arm, multi-stage, randomised controlled platform trial that will accelerate the testing of new anti-tuberculosis and anti-inflammatory drugs for the

optimal treatment of TBM. We envisage the trial being closely linked to the innovative phase 2 and 3 trials of new drugs now being undertaken and planned for pulmonary tuberculosis treatment. Early data sharing and knowledge integration between these trials will be essential if we want them to lead to a substantial fall in tuberculosis morbidity and mortality by 2030.

Transparency declaration:

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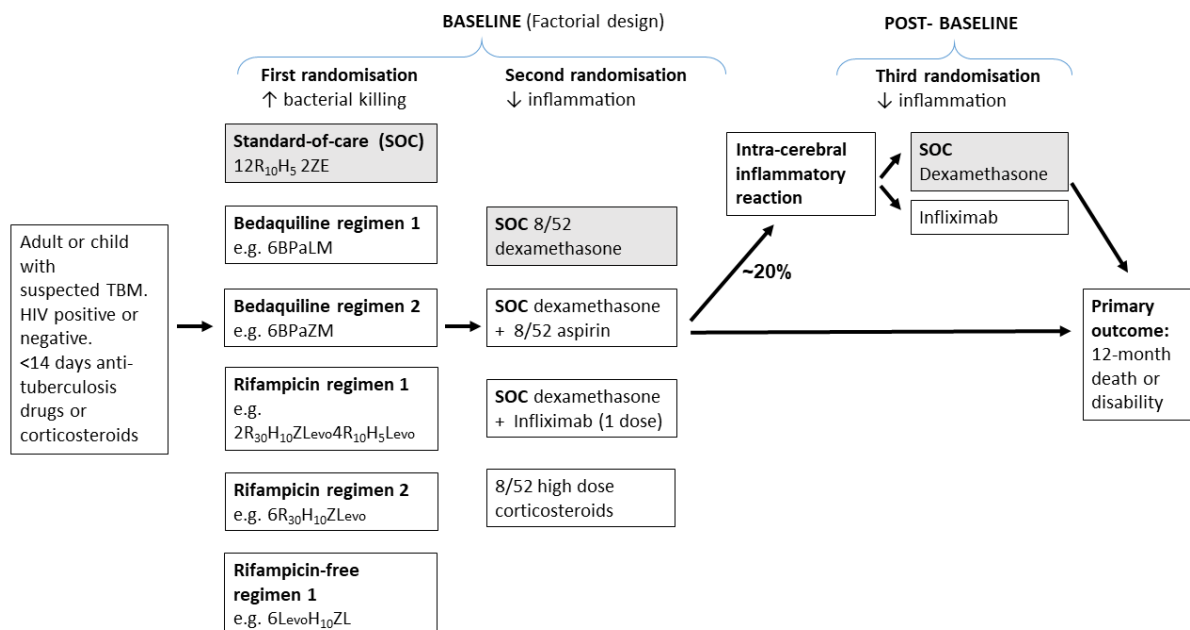
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Figures:

Figure 1. Participant flow for stage one of a global, adaptive, randomized controlled platform trial the best anti-tuberculosis and anti-inflammatory treatment of TBM



Footnote: Details of the interventions/regimens will be decided by the trial investigators. Doses of anti-tuberculosis drugs will be adjusted according to age. For the proposed regimens: R = rifampicin; H = isoniazid; Z = pyrazinamide; L = linezolid; Levo = levofloxacin; M = moxifloxacin; B= Bedaquiline; P=Pretomanid. The larger numbers indicate the duration in months; the subscript numbers indicate the dose (mg/kg/day).