WHO network for HAT elimination

Human African trypanosomiasis: update of the methodological framework for clinical trials

Report of the first meeting of the Development of New Tools subgroup

Geneva, 24 September 2014

World Health Organization

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Abbreviations and acronyms

AE	adverse events
CATT	card agglutination test for trypanosomiasis
CSF	cerebrospinal fluid
DSMB	data safety monitoring board
EMA	European medicines agency
EoT	end-of-treatment
ERB	Ethical Review Board
FDA	Food and Drug Administration
g-HAT	gambiense human African trypanosomiasis
HAT	human African trypanosomiasis
IDM	Innovative and Intensified Disease Management
ITT	intention-to-treat
LP	lumbar puncture
mAECT	mini-anion exchange centrifugation technique
mAECT-BC	mAECT on buffy coat
mHCT	micro haematocrit centrifugation technique
mITT	modified intention-to-treat
NECT	nifurtimox–eflornithine combination therapy
NTD	neglected tropical diseases
PLPHA	post lumbar puncture headache
r-HAT	rhodesiense human African trypanosomiasis
RST	rapid serological test
ToC	test-of-cure
WBC	white blood cell
WHO	World Health Organization

1 Introduction

1.1 Justification for and objectives of the meeting

Researchers involved in clinical trials for the evaluation of new treatment modalities for human African trypanosomiasis (HAT), also known as sleeping sickness, face a number of challenges that are rarely, if ever, encountered in this combination in other diseases. Many of these challenges are related to the fact that both the disease and the populations it affects are neglected and that, prior to 2004, there was no background of generally accepted – and ubiquitously feasible – diagnostic and treatment standards for the planning and conduct of clinical evaluation of new treatment modalities for a disease.

In 2004, the World Health Organization (WHO) organized an expert consultation to establish a methodological framework for clinical trials on HAT in order to facilitate collaboration among research actors and comparison of the data obtained by different groups (WHO 2007). The agreed common criteria were applied from that point by the different researchers, which created a new harmony and a collaborative environment.

During the following decade, thanks to renewed research efforts, new diagnostic tools and new knowledge on assessing treatment outcomes became available (WHO 2013), which may allow improvement of the clinical trial methodology. In addition, the number of HAT cases reported annually to WHO has fallen to fewer than 7000, and the disease has been targeted for elimination. These new facts justify an update of some of the criteria adopted in 2004.

This meeting was framed by the WHO Network for HAT Elimination and it convened specifically the sub-group "Development of new tools", with the following objectives:

- To review and discuss how the new knowledge made available since 2004 could impact the implementation of clinical trials; and
- To update the consensus framework for the planning, conduct and analysis of clinical trials in the future in a way that would promote the acquisition of data that can be readily compared and used in meta-analysis.

1.2 Methodological approach of the meeting

As an initial step, the document of the 2004 WHO expert consultation was circulated among the subgroup members who identified points to update and provided their suggestions.

On the basis of this input, the WHO secretariat produced two working documents which were sent to all the subgroup members:

1. An early draft document: based on the 2004 document and already including many of the comments and suggestions received.
2. A list of Key Questions: arising from the experts' proposals. Some questions were already included in the draft, which was indicated. Under each question, four boxes were provided to enter arguments in support, arguments against, positive outcomes

and negative outcomes foreseen. Experts were invited to create new key questions if considered necessary.

Before the meeting, the Key Questions document containing the consolidated input from experts was sent to all the subgroup members in preparation for the discussions at the meeting.

The meeting took place on 24 September 2014 at WHO headquarters in Geneva, Switzerland. The participants were provided with a working draft 2 (showing track-changes from draft 1) at the meeting. The discussions of the meeting were structured around the Key Questions, which were in turn aligned with the text of the draft document.

The discussion points, having reached consensus at the meeting, were integrated in draft 3 of the document which was circulated afterwards among all subgroup members for verification.

The Agenda of the meeting is included as Annex 1 and the List of participants as Annex 2.

1.3 Scope of the meeting

The discussions and conclusions of the meeting were driven by the need to evaluate the efficacy of new treatment regimens, but are in some cases directly applicable or easily adaptable to the evaluation of new diagnostics.

The conclusions focused on the acquisition of data from clinical trials, since data acquired according to common criteria are a prerequisite for any meaningful comparison between the outcomes of different clinical trials.

With the objective of direct comparability of published data on drug efficacy in mind, a framework for analysis and reporting of the efficacy of the treatment regimens under evaluation was also agreed upon.

The group did not discuss the safety evaluation aspect of HAT clinical trials.

This document concerns gambiense HAT (g-HAT). In the case of rhodesiense HAT (r-HAT), the body of clinical evidence is extremely limited and therefore the elements developed here cannot always be applied in studies of clinical products addressed to r-HAT.

2 Identification of HAT patients for clinical trials

2.1 Screening

The card agglutination test for trypanosomiasis (CATT) on whole blood, a serological test for antibody detection, is used by all national sleeping sickness control programmes for mass screening of the population in areas where *Trypanosoma brucei gambiense* is endemic. Its reported specificity is around 0.97 (Checchi 2011).

Newly developed rapid serological test (RSTs) may be used to replace CATT for screening as appropriate. Their reported specificity is between 0.87 and 0.98 (Büscher 2014; SD Bioline HAT test insert).

At the low HAT prevalence currently observed in most HAT foci, serological tests may result in low positive predictive values. Therefore, before inclusion into a clinical trial, all individuals testing positive on serological tests must undergo parasitological examinations to ascertain the presence of the causative parasite.

Molecular tests can be included, depending on feasibility, in the screening algorithm to increase the overall screening sensitivity and thus accelerate enrolment, i.e. by repeating parasitological examinations (which were initially negative) in individuals with positive molecular test results. For serological tests, individuals testing positive by molecular test should undergo parasitological examinations to confirm the presence of trypanosomes before enrolment into a clinical trial can be considered.

2.2 Diagnosis: general considerations

Only patients for whom trypanosomes are seen in body fluids should be included in clinical trials, to ensure that the efficacy of therapies under evaluation is tested in truly infected individuals.

- The most sensitive parasitological test possible should be used, i.e. mini-anion exchange centrifugation technique (mAECT) (Büscher 2009) or mAECT on buffy coat (Camara 2010) or mHCT (Woo 1971) if mAECT is not available for blood examination; and modified single centrifugation for cerebrospinal fluid (CSF) examination (Büscher 2009; Miézan 2000; Mumba Ngoyi 2013a; Mumba Ngoyi 2013b; Mumba Ngoyi 2014). Enlarged lymph nodes should be punctured for direct examination of lymph-node aspirate.
- Parasitological tests should be performed as soon as possible after sample collection to retain maximum sensitivity. Repeated examinations (if possible, over several days) increase the probability of detecting trypanosomes.
- In order to provide complete parasitological baseline characteristics for the patients enrolled in a clinical trial, blood *and* lymph (when punctionable lymph nodes are present) *and* CSF should be examined for parasites at least once, even if the presence of trypanosomes has already been demonstrated in another body fluid. However, in post-approval phase IV studies on therapies with a well-established risk/benefit ratio, it may be considered to waive the baseline CSF examination in patients with trypanosomes seen in another body fluid (see Annex 3).
- Experience in the field has shown that individuals may be incorrectly categorized as parasitological positives. Confirmation of the presence of trypanosomes in each body fluid by a second staff member is mandatory for clinical trials to reduce the risk of including false parasitological positives in the trial and to obtain accurate data on baseline characteristics.
- Digital recording (taking a picture or video with a mobile phone or other device through the microscope) could be used to allow post-hoc documentation and verification of the images and counts, for quality control purposes. In this case, the study protocol must establish clear rules for the handling of any discrepancies between

the image interpretation and the field results, in terms of patient management, patient classification and data analysis.

- Molecular tests are not a reliable option for confirmation of diagnosis, because currently their analytical performance is not better than the best parasitological tests (Mumba Ngoyi 2014; Mitashi 2013). However, they can be included, depending on feasibility, in the screening algorithm to increase the overall screening sensitivity (see above).

2.3 Staging

- Staging should be based on parasitological criteria and on the white blood cell (WBC) count in the CSF (WHO 2013).
- Neopterin as a CSF marker for second-stage HAT (Tiberti 2012; Tiberti 2013) in clinical trials is not an option at this time, as the supporting evidence is insufficient.
- Lumbar puncture should be performed using disposable spinal needles and following standard procedures of asepsis.
- Post lumbar puncture headache (PLPHA), a well-recognized complication of LP, can be significantly reduced by using atraumatic needles (Davis 2014). Procedural technique may also play a role, with lower rates of PLPHA observed when (i) the needle bevel is inserted parallel to longitudinal dural fibres (Richman 2006) and (ii) the needle stylet is replaced prior to withdrawing the needle (Strupp 1997).
- A volume of at least 5 ml of CSF should be collected, using two or more tubes. It is important that the first drops be discarded to avoid contamination of the CSF with red blood cells.
- Examination of the CSF for both trypanosomes and WBCs should be initiated immediately after collection (Deisenhammer 2006), within 5 minutes, and be completed within 30 minutes of CSF sampling, as CSF trypanosomes may die (and can thus no longer be detected) and CSF WBCs become deformed or disappear quite rapidly after collection of CSF.

The amount of protein in the CSF should not be taken into account for disease staging as abnormally high levels are not specific for second-stage HAT (WHO 2013).

WBC counts