Author’s response to reviews

Title: Cognitive consequences of early versus late antiepileptic drug withdrawal after paediatric epilepsy surgery: study protocol for the TimeToStop (TTS) Trial, a pragmatic randomized clinical trial

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Author’s response to reviews: see over
Dear editors-in-chief,

On behalf of the other authors, we thank you and the reviewers for giving us the opportunity to submit a revised version of the study protocol of our “TimeToStop trial”. We revised the manuscript according to your and the reviewers’ comments, as detailed below.

Furthermore we report a change to the protocol, since we decided to change the primary outcome measure from the CPT (Conner’s continuous performance task) to the “Epitrack Junior”. The following reasons justify this change:

- as opposed to our expectations, none of the first group of children eligible for the study were able to perform the Conner's continuous performance (kiddies) test in a way that scores could be obtained.

- The CPT only probes attention, which is an important but narrow measure of cognitive functioning in patients who use AEDs. The Epitrack Jr (developed by C. Helmstaedter, see reference) is a well validated test that detects disturbances of executive functioning (or “fluid IQ”), including attention, but in a broader sense. The test is particularly well suited to acknowledge adverse effects of AEDs. Furthermore, the test is increasingly applied by several epilepsy surgery European centers; it is translated, freely available, and easy to take.

- We found that the children who could not complete the CPT were able to successfully undergo the Epitrack Jr test.

We changed the trial protocol accordingly, performed a new sample size calculation, and found that the anticipated number of patients needed for the proposed trial did not change.

Below, you will find a point-by-point response to the suggestions and comments. Additionally, we marked the changes made as a consequence of the protocol change. In the revised manuscript, the revisions have been marked in yellow.

We sincerely hope that the revised paper meets the standards of your journal.

Yours sincerely,

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Editorial requests:
1. Please ensure the title conforms to journal style for study protocol articles. The title should follow the format “____________: study protocol for a randomized controlled trial.” Please note that the title in the submission system should match that of your manuscript.

*We changed the title into: “Cognitive consequences of early versus late antiepileptic drug withdrawal after paediatric epilepsy surgery: study protocol for the TimeToStop (TTS) Trial, a pragmatic randomized clinical trial”*

2. Please include the full names of all authors on the title page of the manuscript.

*Done*

3. Please include the date of registration with the trial registration number at the end of the Abstract.

*Done*

4. Please include the names of all ethical bodies that approved your study in the various centres involved. If you do not wish to list them all in the Methods section, please include the list as an additional file and refer to this in the Methods section. Please also explain in your ethics statement (in the Methods section), that you will not begin recruitment in any individual centre until all local approvals have been obtained.

*We added: “In the Netherlands the trial has been approved by the Medical ethical committee of the University Medical Center Utrecht. Other participating centers are in the process of protocol submission and have not yet obtained final approval. Only then, local patient recruitment will start. In the TimetoStop trial, index intervention....” To the first section of the methods at page 4*

5. Please include a list of abbreviations used and their meanings, after the Trial Status.

*Done*

6. Please state that all authors read and approved the final manuscript in the Authors’ Contributions section.

*Done*

7. Please include a figure title and legend section after the reference list.
8. For additional files, please ensure that you list the following information after your reference section in your manuscript:

We don’t have any additional files

**Reviewer 1**

**Major points**

- It is not entirely clear from the methodology when the baseline data for cognition (and the secondary outcomes) will be measured. Only the neuropsychology investigations have this detailed.

  We changed the text into: “We will measure baseline neuropsychological status maximum 3 months before surgery (t1), and thereafter at 12 months (±2months) (t2) and 24 months (±2months) (t3) postoperatively.” Furthermore, we added: “Seizure outcome will be assessed at the moment of randomization, as seizure freedom is an inclusion criterion, at 24 months after surgery, and at 20 months following start of AED withdrawal. This design allows us to assess differences in seizure outcome at equal AED-free intervals for both groups, and at 2 years after surgery irrespective of length of AED freedom” (page 5)

- Could the authors clarify why the timepoints for early (4 months) and late (12 months) tapering of AEDs have been selected? The tapering time (8 months) has some level III evidence base published by some of these studies. Are these timepoints standard practice? Is it local practice? Could AEDs be tapered even earlier, or perhaps quicker?

  The late (reference) starting point of AED tapering – i.e. 12 months – is based on current practice; the median interval between surgery and drug reduction in our retrospective European study was 12.5 month. The 4 months’ time point in the early withdrawal group is selected mainly because of logistical reasons. First, informing parents and recruiting patients needs time. Second, inclusion requires proof of early surgical success, which needs a certain time window to discriminate between acute postoperative (running-down) seizures and true seizure recurrence. Third, in some children clinicians may want to prove completeness of resection by performing a postoperative MRI, for which a minimum follow-up time of a few months is required.

  We added this to pages 4-5

- The one year definition of ‘seizure freedom’ may benefit from further validation (or at least reference to high quality evidence)

  We defined postoperative seizure freedom as Engel 1A or ILAE 1. We added this to the text and added the references that define postoperative seizure freedom to the description of our outcome measure at page 4
• If clinicians have control over the tapering protocol in regard to choice of drug tapered first and also dosing, should this be recorded as a potential confounder in outcome (and if not controlled)?

*We do not control for the order of individual drug tapering, nor for speed of reduction. The randomization procedure, however, is stratified according to medical center, reducing the risk of group differences based on particular center-specific withdrawal preferences. Since we will measure cognitive outcome at a time that patients will be either on full drugs (t=1yr, late group), or fully off drugs (t=1 yr, early group, and t=2 yrs, both groups), the specific order of withdrawal will probably not influence the primary outcome measure. The exact duration of the withdrawal process indeed may influence the time being off-drugs at cognitive evaluation, and thus the cognitive outcome. The randomization procedure, however, is expected to prevent important differences between the two patient groups, and will account for center-specific differences.*

Minor points
• Mixture of American and British English terminology. E.g. ‘center’ (American English), ‘paediatric’ (British English)

*We changed the text into British English, where necessary*

• In the abstract and introduction the authors declare two different ‘ultimate goals’ (1st – aiming for seizure freedom, 2nd – reducing AEDs) – rewording suggested.

*We changed this sentence into: “The goals of intentional curative pediatric epilepsy surgery are to achieve seizure- and antiepileptic drug (AED) freedom” at page 2*

Potential unanswered questions
• Are the authors only considering patients undergoing epilepsy surgery for ‘cure’? Is it relevant to ask whether early AED tapering has other positive effects; eg. to postoperative cognition and development in cases of symptomatic epilepsy surgery (e.g. corpus callosotomy).

*For patients who undergo palliative surgery, the clinician will only try to taper AEDs to reduce side effects, but his or her goal will not be to achieve complete AED freedom, due to the known refractory nature of these seizures. These patients fall outside the domain of our study. Besides, patients who underwent for example a corpus callosotomy, mostly are severely retarded and not able to undertake the neuropsychological assessments we use for primary cognitive outcome measurement.*