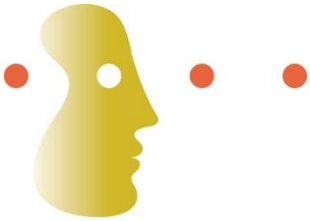

White Paper

Assessing cognitive safety and tolerability in drug trials

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There is increasing pressure on pharmaceutical companies to accelerate the development of safe and effective treatments whilst reducing the risk of failure and encouraging commercial drug differentiation.

In response to this growing demand, Cambridge Cognition has developed two cloud computing products to test cognitive safety and tolerability in drug development.

CTIS-Profile and CTIS-Profile 2$^+$

Clinical Trial Information System – Profile (CTIS-Profile) and – Profile 2$^+$ (CTIS-Profile 2$^+$) are rapid, highly sensitive computerized systems designed for the assessment of cognitive impairment in drug safety trials.

Table 1: Comparison of CTIS-Profile and CTIS-Profile 2$^+$

	CTIS-Profile	CTIS-Profile 2$^+$
Application	Phase I clinical trails	Phase II-IV clinical trials and post marketing
Intended use	Cognitive safety and tolerability assessment	Cognitive safety and tolerability assessment
Age range	18-50 years	Patients of any age and healthy volunteers over 40 years
Cognitive domains	Processing speed Working memory Visual episodic memory Executive function	Processing speed Sustained attention Working memory Visual episodic memory Executive function
Number of cognitive tests	Three	Four
Administration time	Under 15 minutes	20 minutes
Scoring	Automatic	Automatic
Administration	Standardised	Standardised

Introduction

Any drug that crosses the blood-brain barrier can produce cognitive deficits that can interfere with everyday functioning. This includes drugs for Central Nervous System (CNS) indications and non-CNS indications (e.g. oncology drugs, pain drugs, hypnotics, antihistamines, cardiovascular drugs (including statins), HIV drugs, anticonvulsants and antimuscarinics). It is therefore crucial that these risks are quantified during the development process. This is especially true when drugs are intended for populations where cognitive impairments may also be present, such as the elderly, or where drugs are intended for paediatric populations, where cognitive toxicity could have long-term consequences for cognitive development. Conducting special studies to identify adverse effects, such as decreased cognitive function, is in line with FDA reviewer guidance[1] that states that data submissions with such studies will be given more credence than those which do not. CTIS-Profile and CTIS-Profile 2^+ provide the tools to make this assessment. Determining the safety of a compound can be complex and challenging, from both a scientific and an operational perspective. CTIS-Profile and CTIS-Profile 2^+ are designed to support the assessment of compounds for cognitive safety throughout drug development.

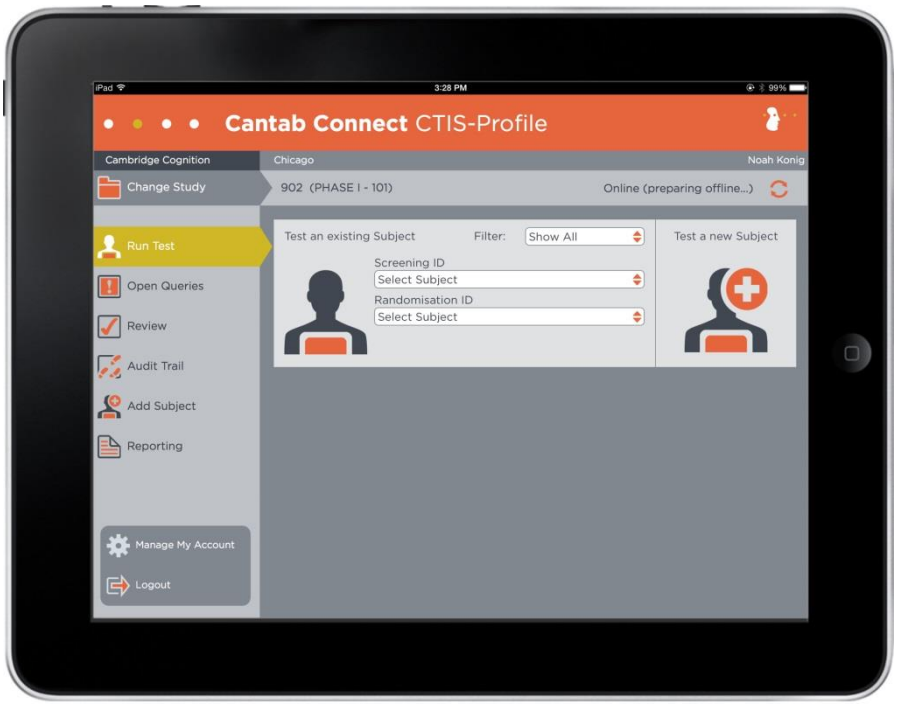
The CTIS-Profile and CTIS-Profile 2^+ products target key cognitive domains commonly affected by pharmacological manipulation, including psychomotor processing speed, visual episodic memory, working memory and executive function. These tests have been employed extensively in clinical trials and academic research. Visual episodic memory is assessed with a paired associates learning test that is sensitive to hippocampal and temporal-frontal network functioning. The spatial working memory and executive function test requires the retention and manipulation of visuospatial information. The self-ordered spatial working memory test has notable executive function demands and measures strategy use. Psychomotor processing is measured using a reaction time test that is an assay for mental and moment reaction times. Finally, the rapid visual information task measures the ability to sustain attention over a period of time, and is a sensitive measure of frontal-parietal function. The data output from all these tests allows you to analyse the relationship between neural system function and any biomarker data, or subjective measures of function or mood. All tests in CTIS-Profile and CTIS-Profile 2^+ are non-verbal and culturally neutral and suitable for use in non-literate or multicultural populations. This also facilitates the use of CTIS-Profile and CTIS-Profile 2^+ in multinational trials as data will be valid regardless of cultural background.

CTIS-Profile and CTIS-Profile 2^+ are supported by 30 years of research and over 1,300 peer reviewed publications. This legacy of research ensures the validity and reliability of test results. Alongside this, the cognitive tests within CTIS-Profile and CTIS-Profile 2^+ have been used in over 135 clinical trials.

CTIS-Profile: Cognitive assessment for Phase I

CTIS-Profile is a cognitive assessment specifically for Phase I trials. There are several advantages associated with assessment of cognitive safety in Phase I. Firstly, Phase I trials assess the widest range of drug doses, allowing collection of valuable information about dose-related changes in brain function and informing decision making regarding the cognitively-safe dose range. CTIS-Profile has a quick test panel that is suitable for repeat testing and monitoring dose escalation effects. Secondly, if serious cognitive impairments are identified in Phase I, cognitive development can then be stopped at this stage, reducing the risk of costly late stage failure. Thirdly, any information about the cognitive effects, whether positive or negative, can help to decide whether other similar compounds should be bought forward from preclinical testing. Finally, if cognitive impairments are identified in Phase I, but development continues, these risks can be monitored in later phases, or when assessing real-life cognitive effects.

The three cognitive tests included in CTIS-Profile are designed to be suitably challenging in order to minimise the risk of boundary effects in Phase I settings. The tests allow repeated testing of subjects, with multiple parallel forms to minimise practice effects associated with familiarity of stimuli. The assessment takes fewer than fifteen minutes to complete in total and is sensitive to cognitive impairment in young and mid-life healthy volunteers.

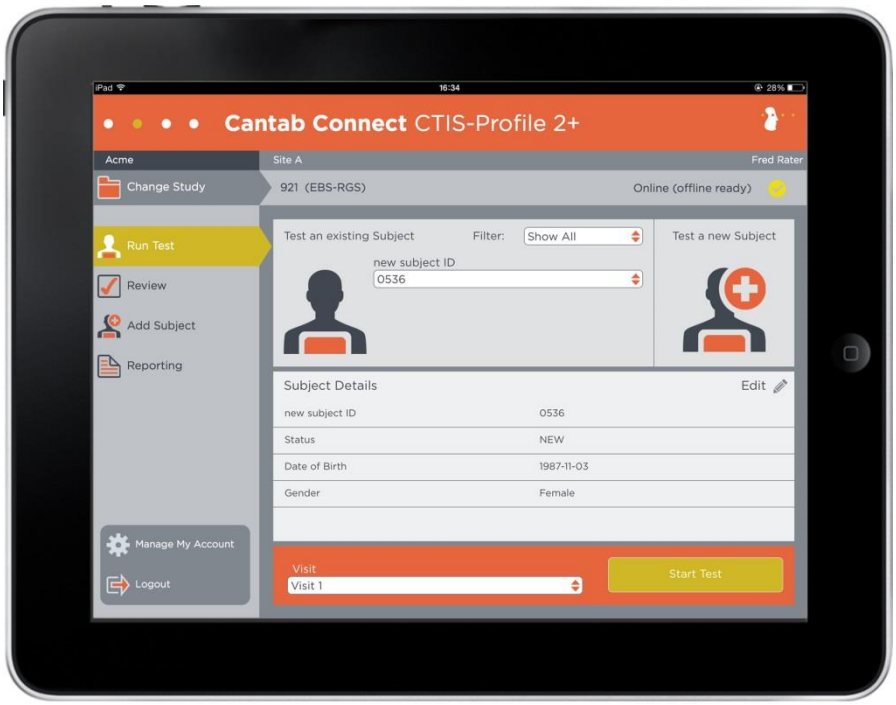


CTIS-Profile 2^{+}: Cognitive assessment for Phase II onwards

CTIS-Profile 2^{+} is designed to characterise the safety and tolerability of a compound in Phase II onwards to post marketing drug trials.

Assessment of cognitive safety in the patient group the compound is intended for is important as drug effects can interact with underlying biology, including disease state. This is especially pertinent if any cognitive risk flags have been identified early on in drug development. Cognitive effects identified can also interact with environmental factors, such as stress or fatigue, to result in potentially serious consequences for a patient. For example, a slowing of reaction time caused by a medication may have little impact under some circumstances. However, in an older adult whose processing speed may already be slowed, this could be more of a cause for concern. Environmental factors, such as fatigue or stress, when cognition is already challenged could further exacerbate the impact of any cognitive adverse effect. For example, a compound that causes only mild impairment under normal conditions is likely to cause more of a concern if it is taken by an older adult driving in poor condition late at night.

The tests included in CTIS-Profile 2^{+} are suitable for use in patients, as well as healthy volunteers. Together the tests take approximately twenty minutes to complete and are all designed to facilitate repeat testing. The tasks are highly sensitive, giving confidence in the cognitive safety of any drug effects in patient populations.



Psychometric properties of CTIS-Profile and CTIS-Profile 2+

The tests within CTIS-Profile and CTIS-Profile 2+ have excellent psychometric properties, with test-retest reliabilities of 0.85 for visual episodic memory, 0.70 for working memory and executive function, and 0.82 for psychomotor speed and reaction time.

Demonstrate cognitive safety

The tests in CTIS-Profile and CTIS-Profile 2+ can be used to demonstrate the superior cognitive safety profile of a new compound compared to existing compounds in order to provide competitive differentiation. For example, in an unpublished Phase IV clinical trial investigating the sedative effects of muscle relaxants, 36 healthy subjects were assessed using the reaction time test, which is one of the tests in both CTIS-Profile and CTIS-Profile 2+, as well as the sustained attention task, which is a test in CTIS-Profile 2+. Performance on both tests significantly deteriorated at the expected time of peak plasma concentration for old compound C and performance on the reaction time task only deteriorated at the expected time of peak plasma concentration for old compound B, but no significant impairment was seen in compound A (Figure 1).

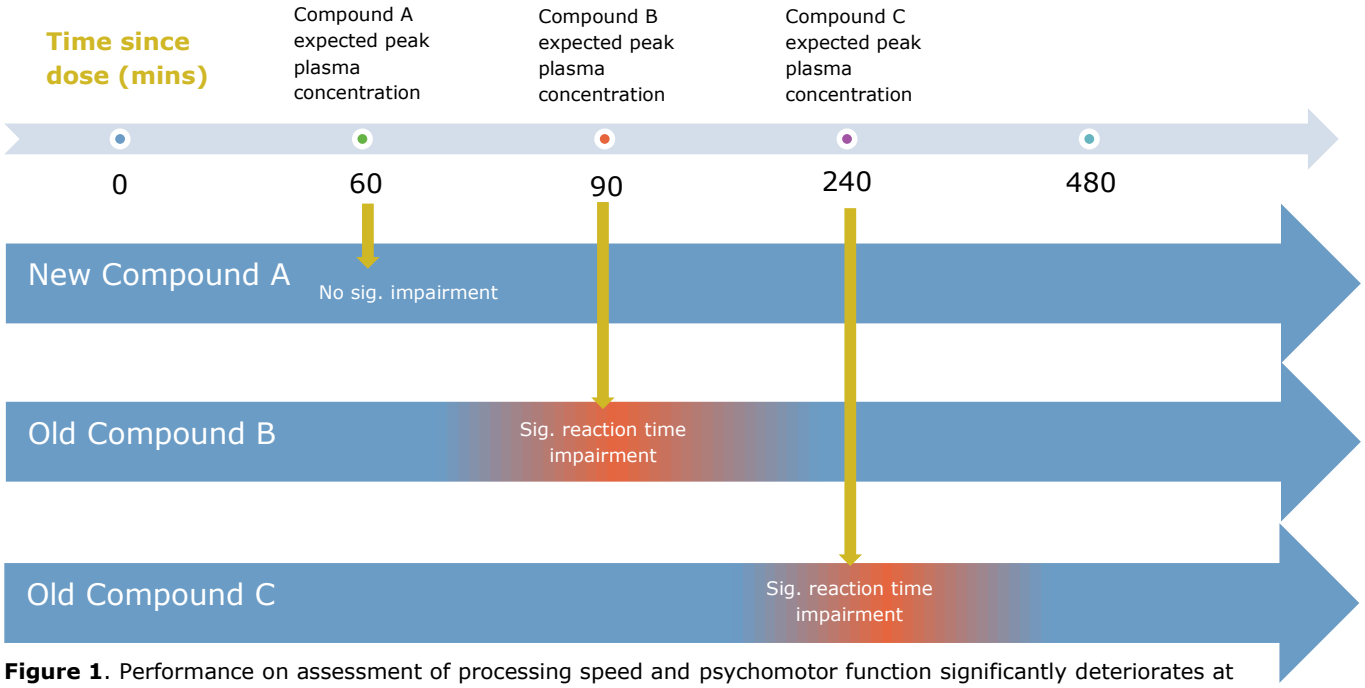


Figure 1. Performance on assessment of processing speed and psychomotor function significantly deteriorates at peak plasma concentrations of Old Compound B and C, but not New Compound A, demonstrating that compound A has a better safety profile.

Define a clinically significant cognitive impairment

One challenge when determining the safety profile of a compound is understanding the clinical significance of observed effects. There are several ways to address this issue. One common way is to use an active control that is known to impair function within the trial as a comparator. Another would be to compare the effect size of the impairment found to the effect size of other compounds that are known to cause impairment.

Figure 2 illustrates the negative effect of acute administration of pharmacological agents in healthy volunteers. On the visual episodic memory domain that is measured in CTIS-Profile and CTIS-Profile 2^{+}, administration of 10mg of diazepam, which is representative of the dose used to treat anxiety, is related to impairment that has an effect size of just over -0.6. This can be compared to the effect of scopolamine, a drug that is known for its deleterious effects on cognition and that is used to model Alzheimer's disease in experimental research. On the visual memory test, scopolamine caused significant impairment (effect size greater than -1). These effects can be used as benchmarks when making decisions about impairments seen in clinical trials.

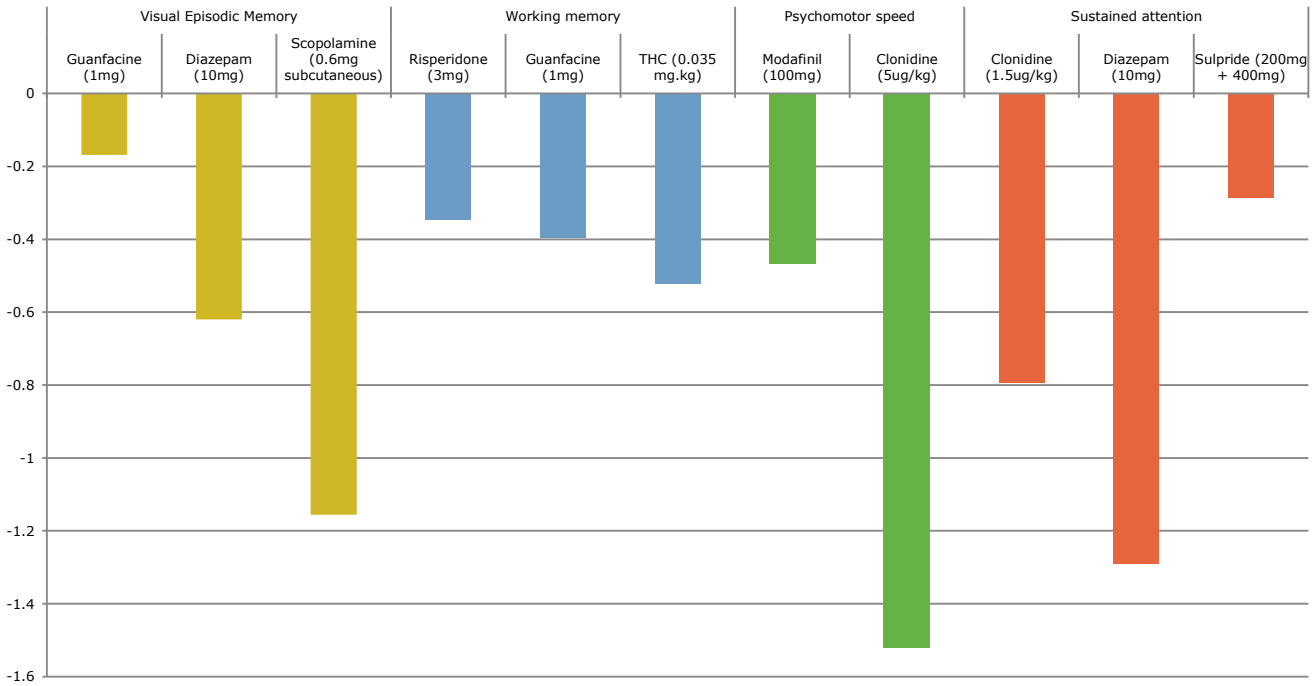


Figure 2. Cohen's d effect size of cognitive impairment following acute administration of Guanfacine[2], Diazepam[3], Scopolamine[4], Risperidone[5], THC[6], Modafinil[7], Clonidine[8] , Clonidine[9], Diazepam[10], Sulpride[11] in healthy volunteers, as measured by the visual episodic memory, working memory, psychomotor speed and sustained attention tests in CTIS-Profile and CTIS-Profile 2^{+}.

Another approach is to equate drug effects to blood alcohol levels or to performance under sleep deprived conditions. For example, Figure 3 shows the synergistic effect of benzodiazepine and antipsychotic medication on reaction time slowing. The unwanted effects on reaction time can be equated to the effect seen at particular blood alcohol concentrations. The combination of drugs was equivalent to being over the drink-driving limit in virtually all jurisdictions, in terms of effects on cognition, at three hours post-dose.

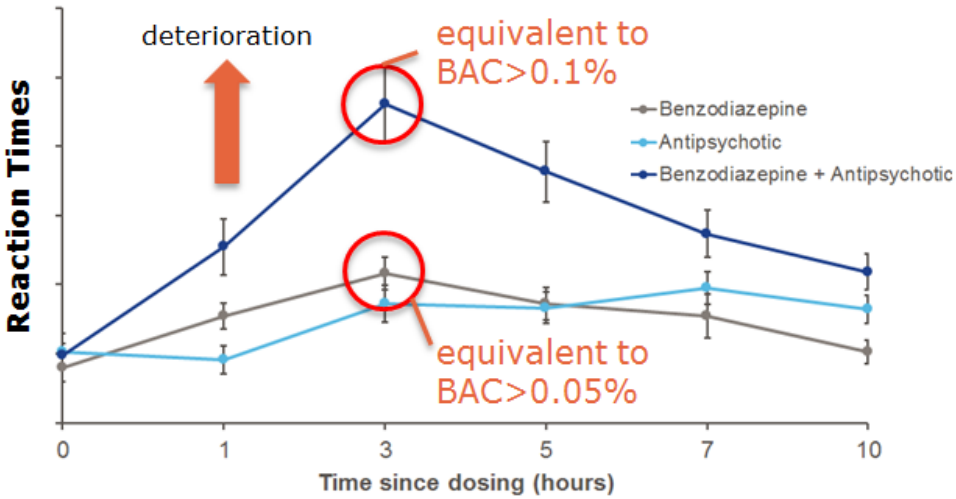


Figure 3. The effect on reaction time of a Benzodiazepine and antipsychotic administered both individually and in combination. At three hours post-dose the effect on reaction time has been equated to Blood Alcohol Concentrations (BAC) that induce the same deleterious effect on reaction time.

Alternatively, a population-based approached can be used, for example using z-scores. This is common in clinical practice where, according to the Peterson criteria, an impairment that is 1.5 standard deviations away from the normative mean is considered to be clinically relevant for the definition of mild cognitive impairment[12]. Figure 4 shows the performance of older adults with MCI and Alzheimer's disease in comparison to normal ageing on the CTIS-Profile tests. In this way, referenced clinical and normative data can be used to determine whether a drug-induced impairment is of cause for concern.

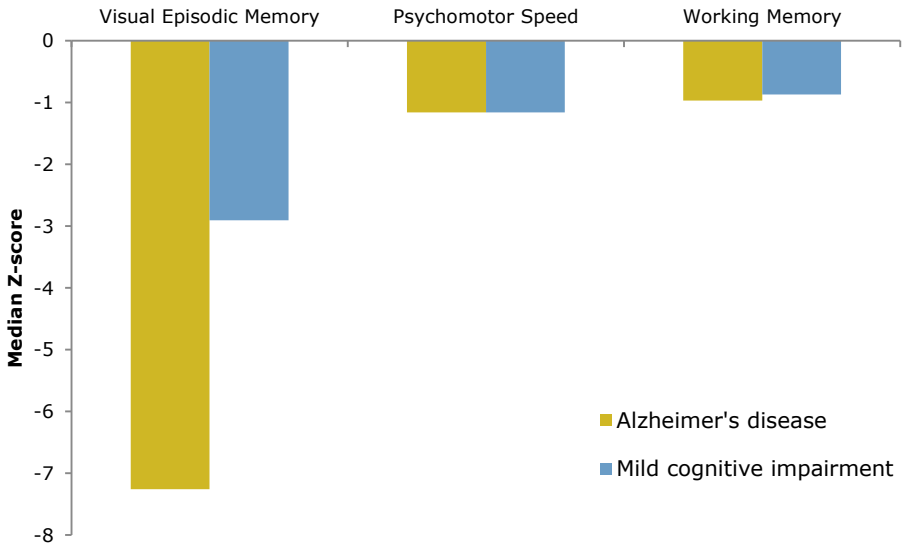


Figure 4. Level of impairment in patients with Alzheimer's disease and mild cognitive impairment compared to an age-matched healthy population on three tests included in CTIS-Profile and CTIS-Profile 2^{+}: paired associates learning (measures visual episodic memory), reaction time (measures psychomotor speed) and spatial working memory (measures working memory and executive function).

Detect adverse cognitive effects in small samples

In some clinical trials setting it is important to be able to measure effects in small samples, such as Phase I studies. All of the cognitive assessments in CTIS-Profile be used to assess cognition in small sample sizes, as data collected in small samples of carefully selected subject groups can closely approximate the group average for large sample sizes. For example, Figure 5 below compares the performance of a group of healthy individuals in a small sample (N=5 and N=8), with a larger sample of N=81, on the visual episodic memory, working memory, and psychomotor speed tests in CTIS-Profile. The test re-test reliability of the cognitive tests is also comparable in the large and small samples (see table 2).

Baseline variability in small sample sizes closely approximates group average for a larger sample

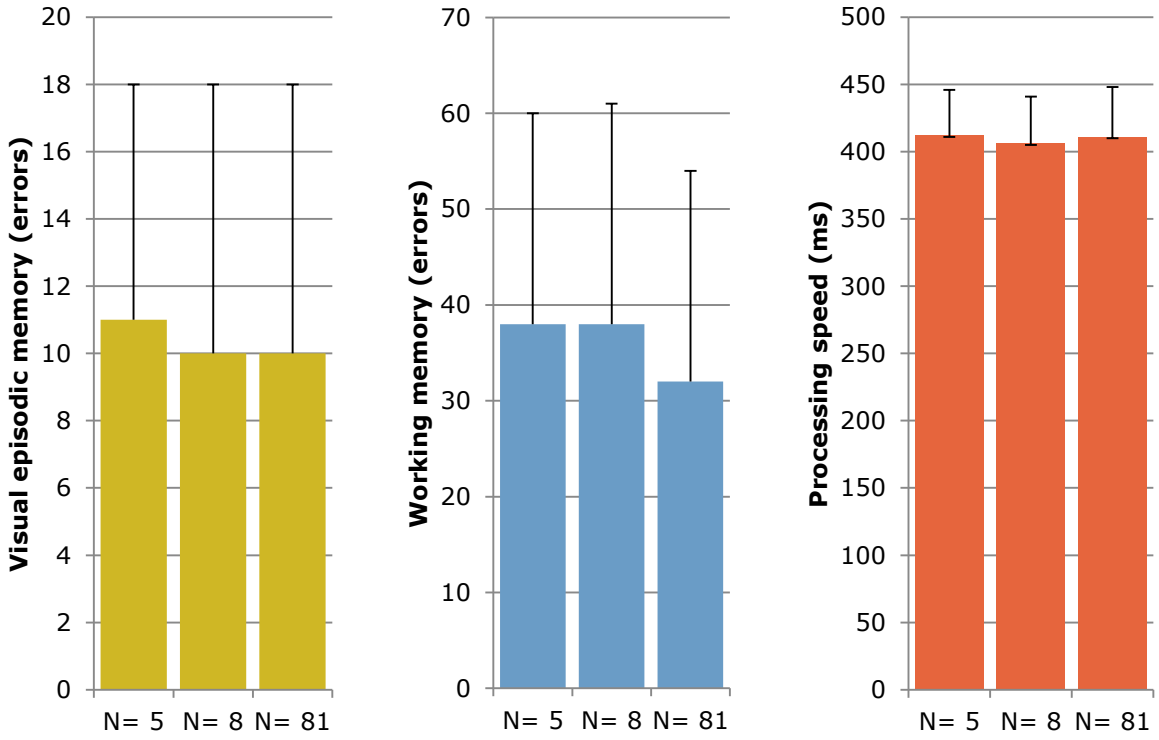


Figure 2. Summary of the baseline variability for the whole group (N=81), and in small sample sizes (N=8 and N=5), for visual episodic memory (a), working memory (b) and processing speed (c). Means and standard deviations are shown.

Table 2: Test re-test reliability of the tests in CTIS-Profile is comparable in small and large sample sizes

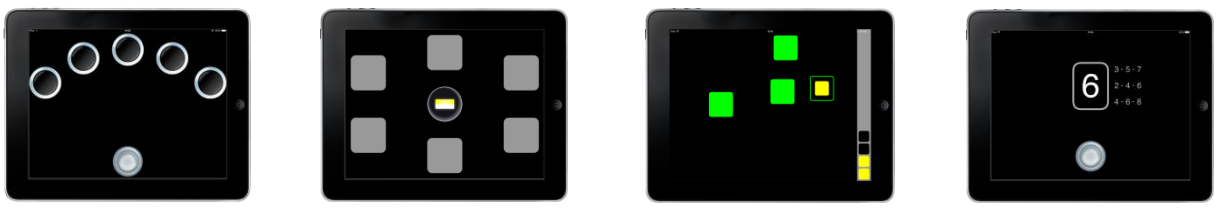
Test-retest reliability	N=5 Pearson's r	N=8 Pearson's r	N=81 Pearson's r
Reaction Time	0.88	0.81	0.82
Visual episodic errors	0.85	0.92	0.85
Working memory errors	0.70	0.83	0.70

Delivered on the Cantab Connect cloud computing platform

CTIS-Profile and CTIS-Profile 2^{+} are delivered on the secure cloud-based Cantab Connect platform, which includes automated scoring and outcome measure calculation, greatly reducing the amount of paperwork and eliminating the risk of human data error. Data quality is further enhanced by online data vigilance, fast data query management, and electronic signatures. Data from multiple hardware systems is synchronised and can be accessed immediately for review in an easy to understand, analyzable format.

The tests are automatically administered in a standard way, including voiceover instructions. This minimises risks of inter-rater variance and consequently maximises data accuracy. It also brings significant time and cost savings as the test administration can be supervised by relatively unskilled site staff, rather than neuropsychologists. The voiceover instructions also permit group testing, as subjects can self-administer the tests, saving time and reducing costs. The tests are engaging for subjects with a visual and interactive testing platform, giving high quality and reliable data. Furthermore, adaptive test formats facilitate assessment of subjects of all levels of ability, unlike traditional non-adaptive cognitive assessment.

Cantab Connect technology is validated for use on iPad Air devices and enables rapid study set-up, seamless remote testing, and secure data encryption on validated hardware, facilitating efficient study execution.



Regulatory compliance

CTIS-Profile and CTIS-Profile 2^+ are designed for GCP-compliant studies. The Electronic Data Capture system complies with the European Clinical Trials Directive 2001/20/EC and meets FDA regulations for computerised systems used in clinical trials and 21 CFR Part 11. The technology is also fully ICH GCP compliant with an established quality management system and 'Best Practice' software development life cycle. CTIS-Profile is ISO 9001, and the software and service processes have been fully audited by sponsors and MHRA.

Summary

Determining the real-life safety of a compound can be complex and challenging, from both a scientific and operational perspective.

Clinical Trial Information System – Profile (CTIS-Profile) is a rapid, highly sensitive computerised system designed for the assessment of cognitive impairment in Phase I drug safety trials. For Phase II onwards, the Clinical Trial Information System – Profile 2^+ (CTIS-Profile 2^+) measures the cognitive properties of compounds in patients and mid-life to older adults, facilitating the objective measurement of cognitive safety to support decision making and drug differentiation.

The highly validated computerised Cantab tests within the products quickly target key cognitive domains commonly affected by pharmacological manipulation, including psychomotor speed, visual episodic memory, working memory, executive function and sustained attention.

The tests in CTIS-Profile and CTIS-Profile 2^+ can be used to demonstrate the superior cognitive safety profile of a new compound compared to in-market compounds or to detect cognitive decline caused by a compound at the earliest possible stage of development.

The information system is delivered iPad via the secure cloud-based Cantab Connect platform, which enables multiple standardised assessments to be conducted globally and data to be automatically scored, synchronised, and accessed in real-time by study sponsors.

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