Improving Alzheimer’s Disease Clinical Research with Bracket

An eBook on the State of Alzheimer’s Disease Clinical Trials and How Bracket is Improving Outcomes with Technology

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# CONTENTS

Introduction .................................................................................................................................................. 3  
Bracket’s eCOA experience in Alzheimer’s Disease ..................................................................................... 4  
Alzheimer’s Disease Clinical Trials Outlook & Challenges ........................................................................... 5  
A Path Forward: What Bracket is Doing ......................................................................................................... 6  
Investing in New Technology ....................................................................................................................... 7  
Expanding Pool of Researchers .................................................................................................................... 8  
Evaluating Clinical Trial Data ..................................................................................................................... 9  
Training and Qualifying Raters ................................................................................................................... 10  
Published Data: Bracket’s Demonstrated Results ........................................................................................... 11  
Initial Pilot Validation of an Electronic Alzheimer’s Disease Assessment Scale ........................................... 12  
Intelligent Clinical Interviews for Alzheimer’s Disease ................................................................................. 16  
Establishing Equivalence of Electronic Clinician-Reported Outcome Measures ....................................... 20  
Conclusion .................................................................................................................................................. 27  
Addendum: References ................................................................................................................................. 28
Introduction

Alzheimer’s disease is deadly and difficult and its impact is enormous.

Every year, the Alzheimer’s Association compiles a report that attempts to quantify the public health impact of the disease, and it’s an essential resource for helping every stakeholder understand the magnitude of the problem. Yet still, understanding the scope of how the disease affects people is difficult.

Overall, the disease prevalence is increasing and there is a huge unmet need for successful Alzheimer’s Disease trials and new therapies. With the highest trial failure rate of any therapeutic area at 99.6%, it is critical that we continue to invest in new and better approaches – and Bracket is accomplishing this by investing in new technology, expanding its pool of researchers, evaluating clinical trial data and training qualified raters.

“This ecosystem must be supported, grown, and coordinated to improve the success of Alzheimer’s Disease trials and development of desperately needed new Alzheimer’s Disease therapies.”

Dr. David. S. Miller
Clinical Vice President
Bracket
Bracket’s eCOA Experience in Alzheimer’s Disease

5,000 SUBJECTS HAVE BEEN EVALUATED USING RATER STATION

45,000 UNIQUE SCALE ADMINISTRATIONS

14,000 SUBJECT VISITS RECORDED ACROSS ALL ALZHEIMER’S STUDIES

25 UNIQUE CLINICAL OUTCOME ASSESSMENTS
Alzheimer’s Disease Clinical Trials Outlook & Challenges

The Alzheimer’s Association and Bracket have been at the forefront of advocating for better care for patients and their caregivers, as well as advocating for more and better research into the disease. There are only limited treatments available for patients with the disease and the R&D track record has been unproductive for the last 15 years. Investment in trials investigating new treatments is at an all-time high and they are encouraging new approaches now being tested.

The top reasons Alzheimer’s Disease clinical trial studies fail:

1. Difficult disease targets
2. Hard to identify patients
3. Many therapeutic approaches have been shown to be ineffective
4. Poor signal detection
A Path Forward: What Bracket Is Doing

At Bracket, we advocate for the use of innovative new technologies to streamline data collection, improve patient engagement and deliver real ROI. We are proud to bring eCOA and Quality Assurance tools to Alzheimer’s Disease research initiatives.
INITIATIVE 1

Investing in new technologies to help diagnose and evaluate patients better

With more experience in Alzheimer’s Disease than any other eCOA provider, Bracket’s Rater Station eCOA platform is based on years of experience working with these difficult, subjective, clinician-reported outcomes and is used to collect patient and caregiver data.

Our tools are built in collaboration with researchers and investigators who work directly with patients and caregivers every day. Published research has shown that our tools can improve the quality of the data in an Alzheimer’s Disease trial, especially compared to traditional paper-and-pencil methods.
INITIATIVE 2

Expanding the pool of researchers qualified to conduct Alzheimer’s disease research

Bracket works to ensure that the research centers and clinicians who conduct Alzheimer’s Disease research are the best possible professionals in their field. We do this by relying on our extensive database of past studies and data analytics to identify individuals who are best positioned to succeed in future research programs.

We also work alongside the Alzheimer’s Association as a member of its Research Roundtable initiative which seeks “to facilitate the development and implementation of new treatments for Alzheimer’s disease by collectively addressing obstacles to research and development, clinical care and public health education.” As a member, we meet semi-annually to gather R&D leaders from across academia and industry to organize new approaches to conducting this research and publish reports on their progress.
INITIATIVE 3

Carefully evaluating clinical trial data to eliminate as much of the noise as possible

Data surveillance programs are essential to ensuring that patients are being appropriately evaluated in a clinical trial. With surveillance experience in dozens of trials, Bracket has developed big data algorithms that can help prevent bad data from propagating by identifying and remediating it early in trials.

There are several good reasons to expand worksheet and ratings reviews to more rigorous audio and video reviews of patient interviews, informant interviews and cognitive testing. Bracket recently released new data on how audio reviews can supplement other, more passive quality assurance measures. Outcomes that rely on subjective patient interviews are still at risk for noise or incorrect data being entered into an EDC. Adding audio reviews of scale administrations enables detection of additional errors that are not apparent on worksheet review alone, thereby data quality during a trial.

Additionally, our Blinded Data Analytics and Quality Assurance programs combine the statistical analysis of raw and derived data with rigorous clinical assessments of the results to identify areas of concern.
INITIATIVE 4

Training raters and certifying they are qualified to participate in research programs

Bracket’s training and certification programs have been in use for 15 years, having qualified more than 16,000 clinicians to participate in Alzheimer’s Disease trials. Our approach focuses on ensuring clinical outcome measures are implemented in a valid and reliable way. Clear and concise training for investigators and raters on how patient information should be collected is essential. Distinguishing between patient and proxy versions is important, as is outlining how the sponsor wants caregivers to provide the information.

These nuances are important and are incorporated into our customized training programs. Through effective training and remediation efforts, researchers can better prepare for these issues when they arise with their patients in a clinical trial.
Published Data: Demonstrated Results

Initial Pilot Validation of an Electronic Alzheimer’s Disease Assessment Scale – Cognitive Subscale (eADAS-Cog): Rationale & Methods

Intelligent Clinical Interviews for Alzheimer’s Disease: How the Addition of Audio Reviews to eCOA Scale Administration Results in Improved Data Quality

Establishing Equivalence of Electronic Clinician- Reported Outcome Measures
Background

The Alzheimer’s Disease Assessment Scale (ADAS) was developed by Richard Mohs, Wilma Rosen, and colleagues, to provide a measure of change in the cognitive and behavioral functions known to be impaired by Alzheimer’s disease. While the original ADAS included both cognitive and noncognitive (behavioral) subscales, most controlled clinical trials employing the ADAS have relied exclusively on the cognitive subscale (ADAS-Cog) to assess the effects of novel interventions on cognitive function. Over the last 20 years, the cognitive subscale, (ADAS-Cog), has become the de facto gold-standard for assessing the efficacy of putative anti-dementia treatments, serving as the primary or co-primary outcome for nearly all phase 2 and phase 3 drug development trials. Given its importance to therapeutic development, there has also been an increasing interest in providing greater standardization and administration consistency of the scale.

- Recently, specific guidelines for establishing equivalency for the development of electronically administered versions of clinician reported outcome (eClinRo) scales such as the ADAS-Cog and paper versions have been proposed and computerized versions of the ADAS-Cog (eADAS-Cog) have begun to be utilized in clinical trials.

- While the eADAS-Cog has been purported to be equivalent to paper in terms of validity, to date, there has not been a prospective trial comparing the electronic and paper versions of the ADAS-Cog in a clinical population.
The goal of the study is to accumulate valid and reliable data in order to determine if scores derived from Bracket’s eADAS-Cog assessment are equivalent to those derived from a standard paper ADAS-Cog in a population of individuals with clinical diagnoses of mild to moderate dementia of the Alzheimer’s type using a prospective methodology.

A single-center, randomized, counter-balanced prospective trial of the eADAS-Cog in comparison to the paper version of ADAS-Cog in men and women ages 50-90 (inclusive) will be employed. For the duration of the study, all consecutive new patients referred to the study site for a clinical evaluation will have the opportunity to participate with the intention of enrolling 25 subjects. The duration of the subject’s participation in the study will last approximately 1 month.

Participants will be screened for eligibility and provide informed consent prior to undertaking any study related measures. If eligible, participants will be randomized to one of two study conditions associated with the order they will receive study measures (see Figure 1, page 14). An investigator, sub-investigator or trained researcher who has previously been trained and certified on both the paper and electronic versions of the scale will administer each of the study measures [MMSE (screening only), eADAS-Cog or paper ADAS-Cog] prior to the subject’s initial clinical evaluation.

Once all study assessments have been administered, the subject will receive a standard clinical evaluation by clinic staff. Clinical staff participating in the clinical evaluation and diagnosis of the subject will be blinded to their performance on the study measures; the subject’s performance on all study measures will not be included when formulating the clinical diagnosis. Those study subjects that meet inclusion criteria will return to the site for two subsequent visits at 2 week intervals at which time they will repeat the study assessments (see Table 1, page 13).
We will investigate the concurrent validity of an eADAS-Cog versus the paper version using Interclass Correlation Coefficients (ICC), Pearson r correlation coefficients and individual t-tests. Longitudinal test-retest reliability between study administrations will be evaluated separately for each mode of administration.

**TABLE 1**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Screening</th>
<th>Baseline</th>
<th>Visit 2</th>
<th>Visit 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Assessment</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eADAS-Cog Administration</td>
<td></td>
<td>X*</td>
<td>X*</td>
<td>X*</td>
</tr>
<tr>
<td>pADAS-Cog Administration</td>
<td></td>
<td>X*</td>
<td>X*</td>
<td>X*</td>
</tr>
</tbody>
</table>

* Subjects will either receive eADA-cog or paper ADAS-cog based on randomization schedule
As electronic versions of validated paper measures become more widely utilized as primary outcome measures in clinical trials, establishing concurrent validity between modalities remains of paramount importance.

**FIGURE 1**

**Conclusions**

Initial Pilot Validation of an Electronic Alzheimer’s Disease Assessment Scale – Cognitive Subscale (eADAS-Cog): Rationale & Methods
Prior research has shown that employing enhanced electronic versions of the ADAS-Cog and MMSE in Alzheimer’s disease clinical trials significantly reduces rater error rates compared to when paper versions of these scales are used. Additionally, the implementation of a customized in-study data quality program can further improve study data quality by monitoring scale administration and scoring to identify instances where raters deviate from proper administration guidelines and/or scoring conventions. When deviations occur, raters are remediated resulting in a decrease in error rates over the course of the trial.

• Data quality programs that reduce rater error are vital to clinical trials, especially Alzheimer’s Disease trials. Given the high failure rate in Alzheimer’s Disease drug development over the past 10+ years, ensuring optimal data quality is paramount. One potential means of addressing data quality in global Alzheimer’s Disease trials is the implementation of an enhanced electronic version of the ADAS-Cog and MMSE (among other scales) coupled with an in-study data quality program.

• In this preliminary analysis, we evaluated whether, and to what extent, adding audio reviews of scale administration to the standard review of electronic scale data resulted in additional identification of rater error and improvement in data quality.
PUBLISHED DATA: DEMONSTRATED RESULTS

Intelligent Clinical Interviews for Alzheimer’s Disease: How the Addition of Audio Reviews to eCOA Scale Administration Results in Improved Data Quality

**Methods**

ADAS-Cog and MMSE ratings were evaluated from a multi-national Alzheimer’s Disease clinical trial. Raters were trained and certified on the proper scale administration and scoring. Initial submissions of scale data from the electronic scales administered to each subject were reviewed along with the corresponding audio. The electronic version of both the ADAS-Cog and MMSE were augmented with internal logic, standardized instructions and scoring conventions taken directly from the respective scale manuals and study specific training curriculum. All raters’ ratings performance was assessed by a calibrated clinician.
PUBLISHED DATA: DEMONSTRATED RESULTS

Intelligent Clinical Interviews for Alzheimer’s Disease: How the Addition of Audio Reviews to eCOA Scale Administration Results in Improved Data Quality

Results

On evaluation of electronic scale data alone, 20% (19/96) of the initial ADAS-Cog submissions contained errors. When the corresponding audios were reviewed, an additional 13% (12/96) of ADAS-Cog administrations contained errors (39% of all ADAS-Cog errors were identified on audio review). For the MMSE, 18% of the 170 (30/170) initial electronic scale data submissions contained errors, and an additional 7 errors or 4% (7/170) were detected upon audio review. Audio review of the MMSE administrations resulted in the identification of an additional 19% of all MMSE errors.

<table>
<thead>
<tr>
<th>Scale</th>
<th>% Electronic Scale Data with Errors</th>
<th>% Audio Reviews with Errors</th>
<th>% All Errors Identified via Audio Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAS-Cog</td>
<td>20%</td>
<td>13%</td>
<td>39%</td>
</tr>
<tr>
<td>MMSE</td>
<td>18%</td>
<td>4%</td>
<td>19%</td>
</tr>
</tbody>
</table>

TABLE 2

Breakdown of All Identified Errors by Review Source (%)

<table>
<thead>
<tr>
<th>Scale</th>
<th>% Total Errors Identified by Audio Review</th>
<th>% Total Errors Identified by Electronic Data Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAS-Cog</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
It is essential that any and all methodologies that could maximize data quality in Alzheimer’s Disease clinical trials be considered. The use of electronic versions of scales that are enhanced beyond their respective paper-pencil versions and coupled with an in-study data quality have proven to reduce rater error. Adding audio reviews of scale administrations enables detection of additional errors that are not apparent on worksheet review alone, thereby further improving data quality over the course of a trial.
PUBLISHED DATA: DEMONSTRATED RESULTS

Establishing Equivalence of Electronic Clinician-Reported Outcome Measures

Background

The use of electronic devices to collect patient-reported outcome (ePRO) measures is becoming increasingly widespread. Studies have shown that ePROs offer advantages over their paper counterparts, including reduced missing data, fewer transcription errors, and increased compliance. Because of the increased acceptance and widespread usage of ePROs, processes to evaluate the equivalence of paper and ePRO scales have been developed. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) ePRO Task Force developed recommendations regarding establishing the equivalence of ePROs with their original paper-based outcome version (PRO).

Dementia clinical research does not rely heavily on the use of PRO measures but instead utilizes more clinician-reported outcome (ClinRO) assessments, where scale ratings are centered upon direct assessment or interviews with patients and/or caregivers. Increasingly, ClinROs are administered in their electronic rather than their original paper format. Although ample evidence exists to support electronic data capture of multiple types (e.g., case report forms and PROs), limited research is available demonstrating equivalence between the electronic and paper versions of clinician-administered measure and the paper version. Like ePROs, there are many benefits of eClinROs including eliminating duplication of data, reducing transcription errors, facilitating data entry, assisting in remote data monitoring, enabling real-time access for data review, and promoting accurate and complete data collection.

Clear guidelines have been established for other aspects of electronic data used in clinical research (i.e., electronic case report forms and ePROs). These guidelines have contributed to the increasing use of electronic capture of individual patient data on case report forms in industry research and resolved much of the debate regarding validation procedures. However, in the absence of industry standards for evaluating the equivalence of eClinROs versus paper, questions regarding the equivalence and validity of electronic versions persist. The purpose of this poster is to propose recommendations to industry, based on the existing recommendations for ePROs, for establishing equivalence between electronic and paper-based ClinROs.
PUBLISHED DATA: DEMONSTRATED RESULTS

Establishing Equivalence of Electronic Clinician-Reported Outcome Measures

Methods

The methods listed below are derived from the guidelines proposed by the ISPOR ePRO Task Force. These guidelines provide a framework for assessing the changes to ePROs and go beyond the requirements set forth by the FDA PRO Guidance.

Levels of Modification

There are 3 levels of modification defined in the ePRO guidance.

MINOR

Can be justified on the basis of logic and/or existing literature. There is no change in content or meaning.

Example: Changing the font from italics to bold.

MODERATE

Based on the current empirical literature, the modification cannot be justified as minor. There may be change in content or meaning.

Example: Requiring the clinician to scroll to see all anchors without any instructions indicating the need to do so.

SUBSTANTIAL

There is no existing empirical support for the equivalence of the modification, and the modification clearly changes the content or meaning.

Example: Removing questions, changing anchors or significantly rewording questions.
Two tiers of scale comparison are recommended and modifications noted should be categorized as described above.

**Content Comparison:** a word-for-word comparison between the original paper scale and the Master Scale Questionnaire [spreadsheet that contains all of the electronic scale content (e.g., question text) that will be displayed on the device].

Items should be classified as:
- **Added:** not included on the paper scale and added to the electronic scale;
- **Removed:** included on the paper scale and removed from the electronic scale;
- **Changed:** included on the paper and included on the electronic scale but modified from original text on the paper; or
- **No change:** the paper scale text and electronic scale text are identical.

**Format Comparison:** examination of the scale as it appears on the device to compare any differences between the paper and the electronic scale.

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**TABLE 1**

Hypothetical Memory Scale Item Content Comparison

<table>
<thead>
<tr>
<th>Item #</th>
<th>Discrepancy</th>
<th>Appearance (Paper)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Instruction</td>
<td>Added</td>
<td>Not Present</td>
</tr>
<tr>
<td>1</td>
<td>Changed</td>
<td>Please circle the employment level that best matches your current situation. You may circle more than one.</td>
</tr>
<tr>
<td>3</td>
<td>Changed</td>
<td>Orientation to Time What is the day today? (Response) _____ Score 0 or 1</td>
</tr>
<tr>
<td>Page 2 header</td>
<td>Removed</td>
<td>Page 2 Memory Questions</td>
</tr>
<tr>
<td>5</td>
<td>Changed</td>
<td>Please write the words recalled below.</td>
</tr>
<tr>
<td>7</td>
<td>Changed</td>
<td>Please copy the design (attach drawing to document)</td>
</tr>
</tbody>
</table>

**TABLE 2**

Hypothetical Memory Scale Format Comparison

<table>
<thead>
<tr>
<th>Tab #</th>
<th>Item(s)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Orientation to Time</td>
<td>All items display on single screen</td>
</tr>
<tr>
<td>2</td>
<td>Orientation to Time</td>
<td>State and Country items display on a single screen, after which scrolling is necessary to see the remaining items</td>
</tr>
<tr>
<td>3</td>
<td>Recall</td>
<td>All items display on single screen</td>
</tr>
<tr>
<td>4</td>
<td>Naming</td>
<td>All items display on single screen</td>
</tr>
<tr>
<td>5</td>
<td>Repitition</td>
<td>All items display on single screen</td>
</tr>
<tr>
<td>7</td>
<td>Comprehension</td>
<td>All items display on single screen</td>
</tr>
<tr>
<td>8</td>
<td>Drawing</td>
<td>All items display on single screen; scrolling required to see instructions to clinician to upload drawing</td>
</tr>
</tbody>
</table>
Adaptation

Two categories of classification have been added to account for differences attributable to adaptation to an electronic device:

Functionality
Change that allows the item to be administered in an electronic format. For example, the use of radio buttons to indicate a response versus circling a response on paper.

Instruction
Change that involves taking information from the scale manual that might not be included on the paper version of the scale, to increase the likelihood that scale administrators adhere to the established scale conventions. Neither functional nor instruction adaptations are believed to alter item interpretability or item scoring but may improve reliability.
Levels of Evidence

Once scale comparison is completed and the levels of modification have been determined, the next step is to provide an adequate level of evidence to support equivalence between the paper and electronic versions of the scale. There are 3 accepted forms of measurement equivalence testing: cognitive debriefing, usability testing, and equivalence testing. Full psychometric testing should be used only when the level of modification is so great that the scale is treated as essentially a new scale.

**Cognitive debriefing**
Cognitive debriefing is a technique used to examine the process by which a target population understands and responds to a questionnaire. This requires 5 to 10 target users and if extensive changes are required, a second round may be necessary.

**Usability and feasibility testing**
Usability testing is used to determine if the target user is able to navigate the device and its software successfully. A simple device may require 5 to 10 target users for testing while a more complex system may require 20 or more. Feasibility testing differs from usability testing in that the target user has the opportunity to field test the scale(s) and provide feedback on the ease of use.

**Equivalence testing**
Equivalence testing is used to measure the similarity between the scores derived from an eClinRO assessment with those obtained using the paper version. The goal is to assess whether there is a statistically significant difference in scores between the two versions.
Results

An important goal with eClinROs is to collect data that have equal or higher reliability than that produced by the original paper scale. As there are no existing guidelines on establishing measurement equivalence, we have set forth guidance for documentation and a route for establishing equivalence of paper and eClinROs (Table 3), based on FDA regulations for creation of PROs and ISPOR recommendations for equivalence evaluation for paper and ePROs.

### TABLE 3

#### eClin RO Equivalence: Instrument Adaptation and Recommended Evidence

<table>
<thead>
<tr>
<th>Classification</th>
<th>Rationale</th>
<th>Examples</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functionality adaptation</td>
<td>Change is made solely for adaptation to electronic format</td>
<td>Nonsubstantive changes in instructions (use of radio buttons rather than circling a response, addition of comment boxes to capture information)</td>
<td>Usability testing</td>
</tr>
<tr>
<td>Instruction adaptation</td>
<td>Addition of instructions from manuals or study-specific conventions not included in the paper scale.</td>
<td>Addition of previously established guidelines (instruction from scale manual informing clinician to read question verbatim)</td>
<td>Usability testing</td>
</tr>
</tbody>
</table>
| Minor modification      | The modification can be justified on the basis of logic and/or existing literature. No change in content or meaning. | 1. Minor changes in format (use of bold vs. italic)  
2. Minor changes in wording of text that did not alter interpretability (using “select item” instead of “underline item”) | Cognitive defriefing; usability testing |
| Moderate modification   | Based on the current empirical literature, the modification cannot be justified as minor. May change content or meaning. | Changes in item wording or presentation that are more significant and might alter interpretability                                                                                                         | Equivalence testing; usability testing  |
| Substantial modification| There is no existing empirical support for the equivalence of the modification, and the modification clearly changes content or meaning. | 1. Substantial changes in response options  
2. Substantial changes in item wording | Full psychometric testing; usability testing |
Conclusions

We have set forth initial good practice recommendations for documentation and a route for evaluating equivalence of paper and eClinROs. Further discussions with key stakeholders are needed to fully define and reinforce best practice for all types of Clinical Outcome Assessments (e.g. eClinRO, eObsRO and ePerfO), to identify areas of commonality and difference in equivalency evaluation.
For help with your next Alzheimer’s Disease clinical trial, contact Bracket.

(610) 225.5900 | Bracketglobal.com
Addendum: References

Initial Pilot Validation of an Electronic Alzheimer’s Disease Assessment Scale – Cognitive Subscale (eADAS-Cog): Rationale & Methods


Intelligent Clinical Interviews for Alzheimer’s Disease: How the Addition of Audio Reviews to eCOA Scale

[1] Miller, D, Feaster, T, Hernandez, A, Abi-Saab, D, Kott, A and Millward, W. The Impact of Electronic Administration of the ADAS-Cog, MMSE and CDR on Clinical Trial Data Quality. Poster presentation at the 2015 Clinical Trials on Alzheimer’s Disease Conference (CTAD), November 5-7 2015, Barcelona, Spain


Establishing Equivalence of Electronic Clinician-Reported Outcome Measures


