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Increasing the Cognitive Screening Efficiency of Global Phase III Trials in Early Alzheimer Disease

The Cognitive Task Force

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Purpose: A Cognitive Task Force (CTF) was established for the MissionAD program with the aim of reducing the screen failure (SF) rate to ~30% and thereby reduce unnecessary subject burden, site burden, and excess trial costs.

Methods/Subjects: The MissionAD program consisted of 2 global phase 3 studies evaluating the BACE inhibitor elenbecestat in subjects with early Alzheimer disease. The CTF monitored and engaged with MissionAD clinical sites to provide support through collegial discussions to maximize the efficiency of the preconsent recruitment phase.

Results: The CTF significantly improved cognitive screening efficiency in the MissionAD program, with a 24% decline in cognitive SF rate for the sites that the CTF contacted. The study-wide 11.5% reduction in cognitive SF rates were likely further driven by wider country-level initiatives in which CTF members held CTF-specific Investigator meetings with the recruitment staff, speaking to all sites on a country level regardless of their recruitment performance.

Conclusions: The establishment of a CTF to support efficient cognitive screening is highly recommended for future Alzheimer disease studies. Additional benefits included improved site relationships, increased engagement in MissionAD and access to a group of cognitive experts for consulting, with a focus on achieving more efficient trial recruitment.

Key Words: Alzheimer disease, clinical trials, screening, cognitive testing, elenbecestat

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Recruiting individuals with early Alzheimer disease (AD) into late-phase clinical trials aimed at determining the efficacy of novel drugs has many challenges. Compared with other similar therapeutic areas, pivotal AD trials are slower to enroll, take longer to complete and are more expensive.[1] Trials in early AD require large samples of individuals who meet clinical criteria for mild cognitive impairment (MCI) or AD dementia with a mild severity and must therefore be conducted in different geographic regions, each with their own cultural and linguistic characteristics, to achieve a timely study enrollment and completion. To identify and enroll individuals whose cognitive and functional impairments are sufficient for classification of MCI or mild AD dementia, recruitment strategies must first raise awareness by having individuals at risk, their family members, or their treating clinicians identify whether there is a concern of or for cognitive decline. Objective screening tools such as cognitive tests can then be applied to confirm whether such individuals have evidence of cognitive impairment and whether this is characteristic of what would be expected in early AD.

From its insidious onset to the slow progression throughout the disease, impairment in episodic memory is the cornerstone cognitive manifestation of both early-stage and late-stage AD.[2] In MCI due to AD or prodromal AD, impairment in episodic memory is qualitatively similar but quantitatively less severe than that in AD dementia. Consequently, impaired memory, defined objectively, is a key criterion of AD in both clinical practice and research.[3–5] Multimodal biomarker technologies provide precise measurements, utilizing cerebral spinal fluid (CSF) or positron emission tomography, of amyloid-beta (Aβ) in vivo which allows clinically classified MCI or dementia to be attributed to AD. Clinical trials of drugs that are designed to forestall AD through acting to reduce brain amyloid accumulation and/or damage, therefore, require that each individual enrolled is classified with abnormally high levels of amyloid in addition to their cognitive deficits consistent with the clinical classification of MCI/prodromal AD or dementia.

In clinical trials of AD, not all individuals screened will be enrolled. While great care must be taken to enroll appropriate participants in clinical trials, it is equally important to minimize the burden and potential risks to individuals from their participation in enrollment procedures, as well as to minimize the cost and time associated with investigating those who will not ultimately satisfy enrollment criteria. In early AD, the most expensive and invasive aspect of enrollment procedures is obtaining

biomarker evidence of abnormal amyloid.[1] Therefore, programs designed to optimize recruitment typically begin with an investigation of appropriate clinical characteristics, move to determine the presence of any characteristics that might exclude individuals from participation or are contrary to the diagnosis of AD and then move finally to assess biomarkers to confirm disease etiology. These stages of enrollment can also be optimized so that they are not independent of one another. For example, while the presence of impairment in episodic memory is important for confirming MCI or mild dementia, the nature or severity of this memory impairment may increase the probability that the individual will be classified as amyloid positive on examination of the biomarkers, whether it be through CSF or imaging. For example, individuals with MCI who show larger impairments in the delayed recall are more likely to be classified as Aβ+.[6] Measures assessing delayed recall are common inclusion criteria for AD clinical trials and form an important part of cognitive prescreening which can help sites triage individuals more likely to meet trial inclusion criteria.

METHODS

Countries, Sites, and Subjects

The Eisai MissionAD program in Early AD was a Phase III program conducted across >500 sites in 29 countries and was designed to assess the efficacy of elenbecestat, a highly selective BACE inhibitor, in MCI and mild AD dementia. Dosing in the MissionAD program was terminated early following a review of unblinded safety data by an independent Data Safety Monitoring Board who concluded that the safety risk outweighed the potential benefit for subjects continuing in the 2 identical trials. At the time of the termination of the MissionAD trials, they were almost fully recruited with >2200 participants randomized into the program. To achieve this the MissionAD program had consented and screened >9700 individuals and at the time, was the largest global program of studies undertaken in this stage of AD. To facilitate recruitment while minimizing clinical trial site and subject burden, as well as controlling trial costs, the protocol defined screening process for the MissionAD studies was divided into stages (referred to as "tiers"). Figure 1 shows the initial tier of screening, Tier 1, which details the necessary cognitive impairment for inclusion into this trial for individuals considered to be at risk for AD. With memory impairment confirmed and clinical disease staging (either MCI due to AD or the early stages of mild AD) confirmed, the subjects proceeded to Tier 2 where additional noninvasive assessments were undertaken. In Tier 3, further comorbid exclusion criteria were applied, and in Tiers 4 and 5 subjects underwent an magnetic resonance imaging then the determination of amyloid level via CSF sampling or amyloid positron emission tomography scan, respectively. For this program, the episodic memory test employed was the International Shopping List Test (ISLT). This was selected due to the availability of normative data (total global normative sample 50 to 95 y = 9500 cases), with country, culture and dialect-specific word lists and computerized scoring and administration.[7] Given that the ISLT is a relatively neoteric measure, in-depth training was conducted at all prestudy Investigator Training Meetings in addition to the Cogstate training required before any in-study administrations of the ISLT to mitigate initial site difficulties with this assessment.

Study Design

The aim of this analysis was to assess the impact of support provided to the clinical sites that aimed to increase the success rate at Tier 1 of the MissionAD screening process, in which protocol mandated objective measures of cognitive impairment were undertaken. Initial stages of recruitment into the MissionAD studies indicated that despite their training and credentialing, some sites had difficulty identifying subjects who met the required episodic memory test inclusion criterion (at least 1 SD poorer performance from age-adjusted norms in immediate or delayed recall on the ISLT),[8] resulting in an unacceptably high screen failure (SF) rate of 53% on the first tier of screening (ISLT 35% SF rate, n = 683, August 2017), which was predominantly being driven by subjects demonstrating too little ISLT impairment (the "worried well"). This was seen at the majority of study sites at the outset of the program, all of whom had varied recruitment and referral sources. Many sites anecdotally tended to start with their own site databases, before moving on to outreach, bringing in new subjects. The subjects within their databases were often cognitively characterized longitudinally, whereas those recruited through outreach required initial cognitive testing and if not, were poorly characterized. There were a broad spectrum of academic sites, neurology practices and private trial sites within the program. These varied widely from country to country, and figures for referrals are not available due to being outside the data collection bounds for the program.

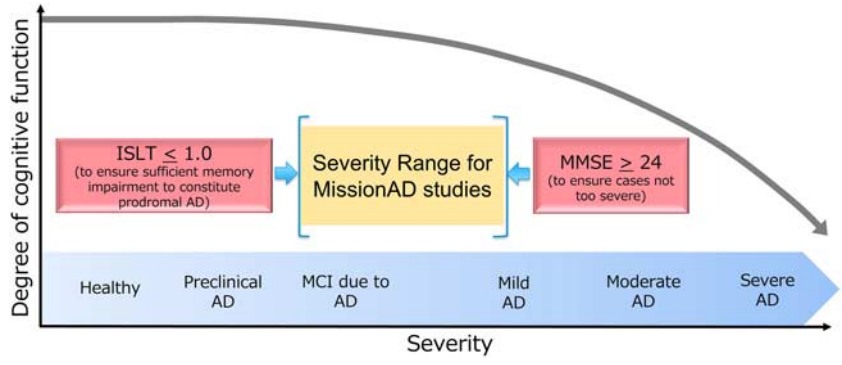

FIGURE 1. Cognitive criteria of subject impairment for inclusion into MissionAD as assessed during Tier 1 of screening. AD indicates Alzheimer disease; ISLT, International Shopping List Test; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

To improve selection of potential subjects who would be consented and thus start Tier 1 screening, the sponsor established a Cognitive Task Force (CTF). The team consisted of a small number of trained neuropsychologists and AD experts situated across companies and regions to provide optimal program support. Team members were assigned on the basis of availability, language ability and locality, with a maximum of 2 members assigned to a site over the course of the program's recruitment duration. The objective of the CTF was to minimize the proportion of subjects who screen failed due to not meeting the protocol requirements on the cognitive components in the first tier of screening [ISLT score 1.0 SD below normative data and Mini-Mental State Examination (MMSE) required score ≥ 24][9] as well as the cognitive and functional staging of the Clinical Dementia Rating (CDR) scale[10,11]; with CDR Global Score = 0.5 and CDR Memory Box score ≥ 0.5. The aim of this work is to describe the interventions developed by the CTF and report their effectiveness on subsequent Tier 1 (cognitive) SF rates within the MissionAD program.

Intervention Methodology

The CTF monitored and directly engaged with the MissionAD clinical sites, with the overarching goal of providing support through collegial discussions to maximize the efficiency of the preconsent recruitment phase. The CTF began by remotely monitoring ISLT, MMSE, and CDR data at a site and subject level, assigning predetermined thresholds for each test and a collective overall threshold allowing the identification of sites that could benefit from a 1:1 discussion with a member of the CTF. The monitoring consisted of combined data reports and algorithms that identified sites that had performed below the predetermined thresholds. Further to the tracking of constituent cognitive data, overall site performance was also considered when determining the CTF's approach. After each site was classified for intervention by the CTF, the site was entered into the database as being under CTF review. In addition, sites that screened with an exceptionally low and therefore good SF rate for Tier 1 were asked to share their approach and encouraged to recruit additional subjects into the studies.

Once a site was identified for CTF intervention, the CTF and study team discussed the approach to be undertaken to ensure that an appropriate level of intervention and tailored strategy was conducted by the team. The CTF began by holding a telephone discussion with appropriate site staff to understand their prescreening methods, subject population, recruitment strategy and site characteristics, with a particular focus on their approaches to any cognitive prescreening. The CTF also advised sites on which prescreening tests could be employed to reduce their Tier 1 SF rates. This included details of appropriate criterion scores that would better predict subject performance on the subsequent study ISLT and the MMSE during postconsent screening as specified in the MissionAD protocols.

On one end of the impairment spectrum for inclusion into the MissionAD studies was the MMSE, which was in place to ensure that subjects did not demonstrate too much impairment as the study was designed to assess an early AD population. To index this before study consent, there was a concern that repeated administration would result in practice effects with improved performance, and as such sites were encouraged to utilize the Montreal Cognitive Assessment[12] rather than the MMSE and were provided guidance on suitable Montreal Cognitive Assessment cutoffs from Roalf et al.[13] To effectively reduce SF rates on the ISLT, the other end of the impairment spectrum, a regional, flexible approach was required, allowing sites to prescreen with episodic memory tests, with emphasis on other verbal list-learning tests which that were validated with normative data for the country-specific languages and were both efficient and easily accessible. For the prescreening test to best predict ISLT outcome, this flexibility had to be balanced with the requirement that the test was measuring the same list-learning episodic memory construct as the ISLT, was published in a peer-reviewed journal and had age-based normative data. The CTF used a site-centric approach for recommendations allowing for culturally appropriate, AD-relevant, normed concordant measures within the country in question to be administered before study consent. The measure was selected based upon site operational processes, language and normative data availability, as well as site staff experience with a particular measure. Where an assessment tool was unfamiliar to the site in question, the CTF provided training on the recommended scale for the staff who would undertake the administration. The brief form of the California Verbal Learning Test, Third Edition (CVLT-3-BF)[14] was provided to several sites due to its ease of acquirement, length of administrations and inexpensive cost. Other measures without normative data comparisons required the CTF to provide electronic z-score calculators to the sites which took raw scores on the chosen prescreening memory measure (ie, the Free and Cued Selective Reminding Test[15] or Rey Auditory Verbal Learning Test)[16–18] and gave z-scores for comparison to the MissionAD inclusion criteria for episodic memory impairment (at least 1 SD poorer performance from age-adjusted norms in total or delayed recall on the ISLT).

Sites with low SF rates (below the threshold for CTF intervention) typically conducted thorough prescreening on potential subjects or had recent (< 3 mo old) preexisting cognitive testing information within their site's database. Success for the intervention by the CTF was measured by the reduction in SF rates on the tests that comprised the first tier of screening: the ISLT, MMSE and CDR. With the implementation of the CTF beginning 4 months after the first subject had been screened and with ~2% of the subjects randomized, metrics were determined for 98% of the program's recruitment period. Once a site had screened at least 5 subjects, SF rates were calculated for each individual tier 1 test, the overall Tier 1 SF rate and the overall site SF rate. *t* tests were run on the pre-SF and post-SF percentages to obtain statistical significance for this intervention.

RESULTS

In total the MissionAD program consented and screened > 9700 subjects across 29 countries. Overall, 141 sites out of the total of 526 within the program (26%) were contacted by the CTF at some point during the enrollment period. Forty-four of the 141 (31%) sites were contacted by the CTF on > 1 occasion. Overall, 76% of contacts were made due to a high site SF rate on the ISLT, 17% due to SFs on the MMSE (ie, scores <24), and 7% due to general site issues or poor recruitment rates. When sites were contacted on > 1 occasion, the latest date of intervention was used for the postintervention metrics.

The regional distribution of the contacts and interventions made by the CTF approximately mirrored that of the distribution of the study sites across the program. The majority of contacts were made with sites located in the United States (Table 1).

TABLE 1. Country Breakdown of CTF Intervention

	Argentina	Australia	Canada	Chile	Czech Republic	Denmark	Finland	France	Germany	Italy	Mexico	Poland	Portugal	South Africa	Slovakia	South Korea	Spain	UK	United States
Total interventions by CTF (%)	3	1	9	1	1	1	1	1	2	1	1	1	1	1	2	1	6	7	60
No. sites	14	11	14	5	10	3	4	15	20	15	4	12	5	5	8	19	22	24	170
Proportion of total screens (%)	1.8	1.6	3.4	0.7	2.2	1.2	0.4	1.4	2.1	1.3	0.2	4.2	0.8	0.9	1.6	2.4	3.2	9.3	46.2

CTF indicates Cognitive Task Force.

Among sites contacted by the CTF, total Tier 1 SF rates were reduced from 67% precontact (n = 1583 screened; 1067 SF) to 43% postcontact (n = 907 screened; 387 SF), yielding a 24% decline in the Tier 1 SF rate ($P = 1.63e^{-11}$). Among these sites, MMSE-related SF rates were reduced from an average of 21% precontact to 12% postcontact ($P = 1.17e^{-5}$) and ISLT-related SF rates were reduced from 47% precontact to 31% postcontact ($P = 3.85e^{-13}$). Overall study metrics revealed that the Tier 1 SF rate started at 53% upon the inception of the CTF and was reduced to 41% at the end of the study screening process when program recruitment was closed. This was determined at an individual site-level rate but not as an overall rate program-wide rate. This was due to the staggered interventional approaches and varying numbers of active sites at a given timepoint, which did not allow for CTF versus non-CTF site intervention comparisons. To note, the final 4 weeks of screening in December 2018 of 588 subjects yielded a SF rate on the ISLT of just 19.9%.

Site-level SF rates are shown in Figure 2. These results drove the overall study SF rate down by 5% during the year 2018. This was seen by an 8% drop in the study-wide SF rate at the first tier of screening during this time period. Figure 3 demonstrates the increased number of calls made by the CTF and the reductions in study-wide SF percentages. If the SF rate had remained at 86% from January 2018 to the time, the studies were terminated, this would have resulted in a need to consent and screen at minimum an extra 2820 subjects and an approximate extension of the study recruitment period by 8.5 months to accommodate this requirement.

CTF interventions with sites across the globe uncovered unique referral patterns and cultural differences in enrollment practices. Regional variation was seen in the cognitive screening data which was mirrored by the type of support given by the CTF (Table 2). Analyses of variance showed significant differences on the model for ISLT immediate or total score with a range of 0 to 36 ($F_{4,8619} = 37.82$, $P < 0.01$), ISRL which is the ISLT delayed recall with a range of 0 to 12 ($F_{4,8619} = 71.95$, $P < 0.01$), MMSE ($F_{4,9051} = 2.52$, $P = 0.04$) and CDR—Sum of Boxes (SB) ($F_{4,6411} = 18.82$, $P < 0.01$). Post hoc analysis indicated significant regional differences on the ISLT immediate recall and delayed recall were being driven by a less impaired population in North America (Canada and the United States) compared with all other regions ($P < 0.05$ for all relationships). South America (Argentina, Chile, and Mexico) screened significantly more impaired subject populations on the ISLT compared with all other regions. MMSE totals showed little variation between the regions except for South America showing less impairment compared with Europe (Austria, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Poland, Portugal, Russian Federation, Slovakia, Spain, and the UK) and South Africa and Asia Pacific (Australia, China, Singapore, South Korea, Taiwan) ($P < 0.05$). CDR-SB regional differences were exclusively driven by higher scores from North America and Europe/South Africa compared with those from Japan, Asia Pacific, and South America (Europe/South Africa only) ($P < 0.05$).

DISCUSSION

The primary role of the CTF was to reduce the Tier 1 SF rates due to the cognitive and clinical staging requirements of the MissionAD studies. As a consequence, this would reduce unnecessary subject and caregiver burden,

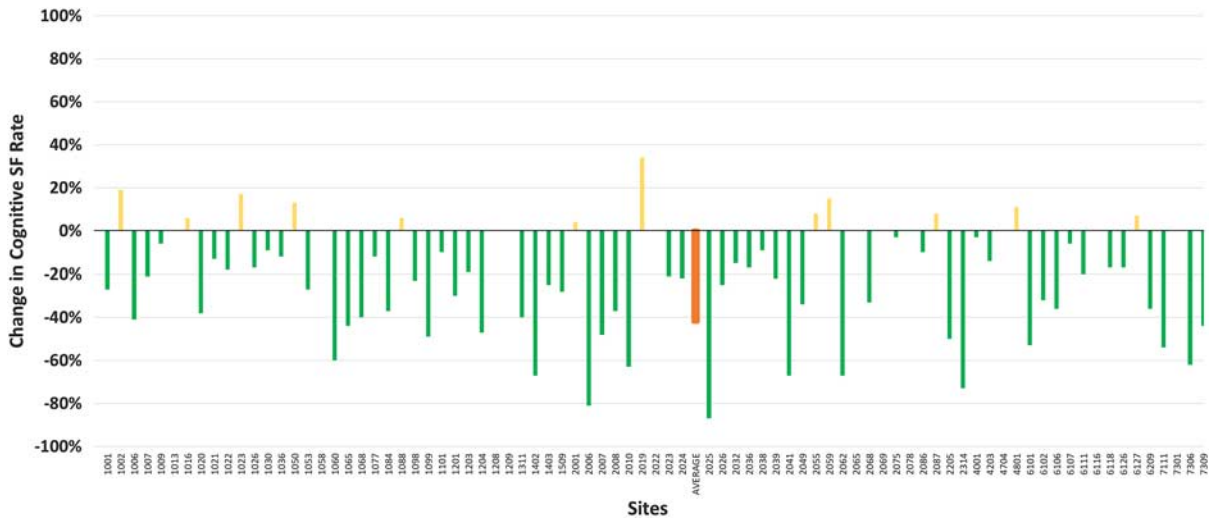

FIGURE 2. Site-level screen failure (SF) rate change.

clinical site burden, and trial costs as well as shorten the duration of trial enrollment, thereby reducing the time to obtaining the results from the studies. The CTF significantly improved cognitive screening rates and efficiency in the MissionAD program, with a 24% decline in Tier 1 SF rate for the sites that the CTF contacted. The global 11.5% reduction in Tier 1 SF rates were also likely driven by wider country-level initiatives in which, CTF members held CTF-specific meetings with recruitment staff, speaking to all sites on a country level regardless of their recruitment performance. Additional benefits of this approach included improved site relationships from increased interaction, increased engagement in the MissionAD program and access to a group of AD and cognitive experts for consulting, with a focus on achieving more efficient trial recruitment.

As the first global early AD clinical program utilizing the ISLT for study inclusion, the MissionAD studies demonstrated the successful utilization of this measure to recruit the target subject population. However, overall referral patterns were shown to differ by region and cognitive profile. Sites in western countries (North America, Europe/South Africa) tended to consent and screen subjects with less objective impairment in general, needing help to prescreen and exclude the "worried well" with suitable episodic memory measures before entry into the study (which was the initial reason for establishing the CTF). Conversely, sites in eastern regions of the world (Asia Pacific and Japan) tended

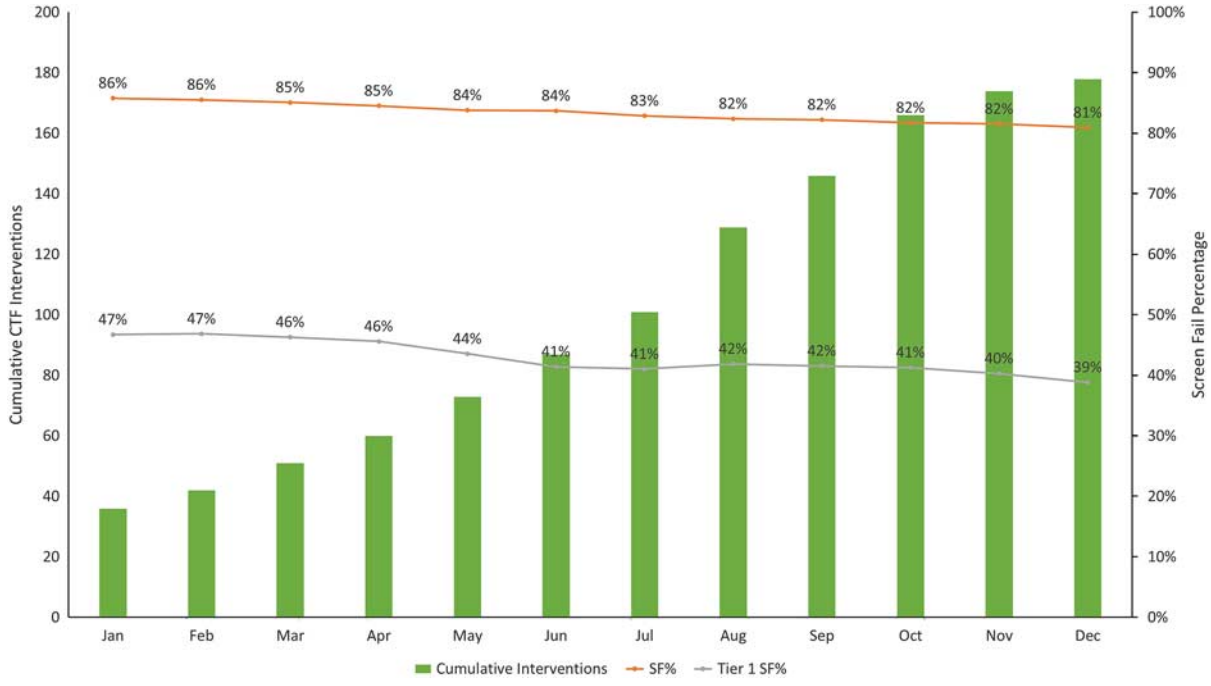

FIGURE 3. Study-level screen failure (SF) rates and Cognitive Task Force (CTF) interventions in calendar year 2018.

TABLE 2. Average Score by Region and Cognitive Indices

	N	ISLT Immediate Recall z-score	ISLT Delayed Recall z-score	N	MMSE Total	N	CDR-SB
North America (NA)	4399	−1.16 (1.05)	−1.09 (1.11)	4486	25.93 (3.1)	3147	2.54 (1.3)
Europe/South Africa (E&SA)	2628	−1.41 (1.07)	−1.42 (1.16)	2725	25.86 (2.9)	1992	2.59 (1.3)
Japan	927	−1.34 (1.01)	−1.57 (1.29)	1109	25.94 (2.8)	699	2.25 (1.0)
Asia Pacific (APAC)	432	−1.44 (0.97)	−1.65 (1.18)	484	25.78 (2.7)	359	2.15 (1.2)
South America (SA)	237	−1.68 (1.03)	−1.65 (1.15)	252	26.43 (2.4)	219	2.34 (1.3)

CDR-SB indicates Clinical Dementia Rating—Sum of Boxes; ISLT, International Shopping List Test; MMSE, Mini-Mental State Examination.

to screen subjects that were too impaired, and therefore, these sites needed support to identify suitable MMSE-like measures before the screening. Interestingly the CDR-SB scores by region showed the opposite of the objective memory measure, which perhaps may be related to cultural differences in caregiver's reporting of the subject impairments to clinicians and raters. Interestingly, the comparative impairments seen in CDR-SB scores in Europe/South Africa (E&SA) and North America, when compared with a lack of objective memory impairment, may represent caregiver reporting of impairment in day-to-day function. This could also speak to a lack of ecological validity within current neuropsychological tests, which is only uncovered within interviews or Activities of Daily Living scales. Solving this underreporting of impairment, as seen in the Asia Pacific region (including Japan), requires sensitive interviewing techniques that may go further than standard practice. These techniques would have the ultimate goal of uncovering the true nature of impairments that are borne out in objective cognitive measures, which is already how the CDR is designed, albeit with very much a western population in mind. Alternatively, it could also reflect an overreporting from caregivers in these regions when compared with actual objective memory and global impairment shown on the other cognitive scales. Furthermore, the lack of comparative differences on the MMSE seems to suggest worldwide uniformity on this measure both in-clinic and for trial screening as seen in more detailed analyses of the MMSE data from this program.[19]

The clear regional disparities show the need for careful country selection and training when conducting multi-country clinical trials in this indication. In these studies, countries and sites were selected based upon a broad range of criteria; including regulatory needs, prior performance, recruitment ability, potential subject population, and the availability of suitably qualified raters for the cognitive assessments; there was a good balance of academic, hospital, private and professional contract clinical sites overall. The CTF, therefore, proved to be effective in dealing with regional or country variability in the processes that preceded referral and recruitment. This approach may be more parsimonious than seeking to develop study-specific and country-specific strategies for recruitment, which could act to increase variability in study samples.

While the ISLT is a word recall task, the ecological validity of the randomly-generated word list is more akin to everyday deficits subjects may be experiencing and, therefore, a good measure of day-to-day memory performance. This carries many divergent qualities to other measures more commonly utilized within clinical trial inclusion criteria, such as the Logical Memory.[20] The Logical Memory story recall is argued to be clustered into chunks of information, therefore, when compared with other episodic memory measures, giving the recall of the story a slightly elementary slant. This is thought to allow subjects with greater executive deficits, who's the ability to "cluster" is impaired, improved recall on this paradigm. In contrast to this are verbal list-learning measures, where the random nature of the word lists requires subjects to utilize their ability to cluster independently of the test paradigm. Prior work has shown indices of both story recall and list-learning recall to have comparable SF rates (Repeatable Battery for the Assessment of Neuropsychological Status Delayed Memory Index, 33%; ISLT, 30%).[21] However, the MissionAD program showed slightly higher initial cognitive SF rates (ISLT, 35%, August 2017) than prior research across both paradigms.[21,22] As shown with this methodology, the results from this approach show ways to continue to improve clinical trial efficiency and markedly reduce SF rates on cognitive measures within clinical trials. This clear improvement upon prior SF rates shows the utility of a CTF within a clinical trial utilizing cognitive inclusion criteria.

Importantly, the interventions undertaken by sites following CTF contact often required a greater level of prescreening for subjects, which did increase initial site burden. However, this more detailed prescreening allowed sites to ascertain the subject's level of cognitive impairment before a detailed consenting process. And while a subject may not have been suitable for this program, there would still be the potential for other clinical trials in this field, with 90% of sites running multiple clinical trials in AD. The argument that this increase in site burden is undue is unfounded. The additional information on subjects gleaned from undertaking standard neuropsychological measures allowed for the proper triaging of potential study subjects and alleviated the need to waste time going through a consenting process, only for the study subject to SF at the first hurdle.

Within the field of AD clinical development, large scale trials are extremely costly and require lengthy recruitment periods to achieve the required study population. As a result, these clinical trials may be out of reach for the majority of small-to-midsize pharmaceutical research companies. Any process improvement that enhances the ability to make these large scale trials more efficient and cost-effective will aid the investigation of a greater number of research compounds and enable the field to learn more about potential mechanisms involved in the disease. Improving cognitive SF rates does not only have cost implications; it reduces individual subject and study partner burden and offers significant alleviation of site staff resources over the course of a study. Most importantly, it should decrease the time to achieve target enrollment into the interventional clinical trials needed to establish the safety and efficacy of novel treatments. Overall, the CTF consisted of a small number of neuropsychology

professionals, and the cost of the CTF was more than offset by the improved screening efficiency and shorter recruitment period required as a result. In conclusion, the establishment of a CTF to support efficient cognitive screening during subject recruitment for future studies in AD and other indications with cognitive or a neuropsychological testing component to eligibility criteria is highly recommended.

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