Received: 24 March 2022 | Revised: 1 September 2022 | Accepted: 5 October 2022

DOI: 10.1002/alz.12843

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE

A public resource of baseline data from the Alzheimer's Prevention Initiative Autosomal-Dominant Alzheimer's Disease Trial

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Abstract

Introduction: The Alzheimer's Prevention Initiative Autosomal-Dominant Alzheimer's Disease (API ADAD) Trial evaluated the anti-oligomeric amyloid beta (Aβ) antibody therapy crenezumab in cognitively unimpaired members of the Colombian presenilin 1 (PSEN1) E280A kindred. We report availability, methods employed to protect confidentiality and anonymity of participants, and process for requesting and accessing baseline data.

Methods: We developed mechanisms to share baseline data from the API ADAD Trial in consultation with experts and other groups sharing data from Alzheimer's disease (AD) prevention trials, balancing the need to protect anonymity and trial integrity with making data broadly available to accelerate progress in the field. We pressure-tested deliberate and inadvertent potential threats under specific assumptions, employed a system to suppress or mask both direct and indirect identifying variables, limited and firewalled data managers, and put forth specific principles requisite to receive data.

Results: Baseline demographic, PSEN1 E280A and apolipoprotein E genotypes, florbetapir and fluorodeoxyglucose positron emission tomography, magnetic resonance imaging, clinical, and cognitive data can now be requested by interested researchers.

Discussion: Baseline data are publicly available; treatment data and biological samples, including baseline and treatment-related blood-based biomarker data will become available in accordance with our original trial agreement and subsequently developed Collaboration for Alzheimer's Prevention principles. Sharing of these data will allow

exploration of important questions including the differential effects of initiating an investigational AD prevention therapy both before as well as after measurable Aβ plaque deposition.

KEYWORDS
Alzheimer's disease, amyloid, antibody, data sharing, magnetic resonance imaging, positron emission tomography, presenilin 1, primary prevention, secondary prevention

1 | INTRODUCTION

The Alzheimer's Prevention Initiative (API) was established in 2008 to accelerate the evaluation of promising prevention therapies in persons at increased risk for Alzheimer's disease (AD) and provide a shared resource of prevention trial data and biological samples.[1–7] The API Autosomal-Dominant Alzheimer's Disease (ADAD) Prevention Trial (NCT01998841)[7] received grant support from the National Institutes of Health (NIH) as part of the 2012 National Plan to Address Alzheimer's Disease, introducing novel pre-clinical AD prevention strategies that have been embraced and extended by both academia and industry to evaluate AD-modifying treatments in persons at genetic and/or biomarker risk for the disease. The API ADAD Trial is intended to be potentially license-enabling, support the development of theragnostic biomarkers that could further accelerate the evaluation and approval of prevention therapies, and establish public–private partnerships to support this endeavor. The API ADAD Trial included a commitment to provide a public resource of data and biological samples after trial completion.

After the trial was announced and two other AD prevention trial programs were established, leaders of the API, the Dominantly Inherited Alzheimer's Network (DIAN), the A4 Trials Program, the Food and Drug Administration, National Institute on Aging (NIA), Alzheimer's Association, and F-Prime Biomedical Research Initiative established the Collaboration for Alzheimer's Prevention (CAP) to exchange ideas about how to advance AD prevention research; address relevant scientific, ethical, and logistical challenges; and publish principles for sharing pre-randomization data, treatment data, and biological samples in prevention trials.[8] The NIH has made clinical trial data sharing a requirement in grant-supported trials and there is growing momentum for sharing data and samples in all industry-sponsored clinical trials. Emphasis was placed on developing data and sample sharing strategies that protect research participant confidentiality, guard against genetic risk disclosure, and preserve trial integrity and chances for regulatory agency approval. Our baseline data and sample sharing plans have benefited from our interactions with leaders from the A4 Prevention Trial[9,10] and DIAN,[11,12] patients and families affected by AD, and the API ADAD Trial's Ethics and Cultural Sensitivities Committee.[7]

As detailed previously,[7,13] the API ADAD Trial is a randomized, placebo-controlled clinical trial of the anti-oligomeric amyloid beta (Aβ) monoclonal antibody treatment crenezumab in 252 cognitively unimpaired Colombian presenilin 1 (PSEN1) E280A mutation carriers and non-carriers from the world's largest ADAD kindred (API-Colombia).[14,15] The mutation carriers are virtually certain to develop AD and progress to mild cognitive impairment (MCI) and dementia at the respective median ages of 44 and 49.[16] Like other ADAD mutation carriers, PSEN1 E280A mutation carriers demonstrate biomarker evidence of Aβ plaque more than 25 years before the onset of dementia, followed by tau tangle deposition and neurodegeneration.[14–19] The API ADAD Trial includes participants within about 15 years from carriers' median age of MCI onset at the time of enrollment and who have not received information about their genetic risk who receive 60 to 96 months of double-blind treatment using a common close design. The trial has recently concluded.

In addition to evaluating the efficacy, safety, and tolerability of crenezumab, the trial was designed to provide a better test of the amyloid hypothesis than largely unsuccessful trials in later disease stages. The trial explores the effects of treatment in the primary and secondary prevention of AD; aims to clarify the extent to which the treatment's effects on biomarkers are associated with subsequent clinical benefit (i.e., inform the extent to which AD biomarker endpoints might serve as surrogate endpoints in future trials); and support the detection, tracking, and study of preclinical ADAD. The baseline data collected to answer these important questions are publicly available as a resource for other researchers.

The API ADAD Trial presents challenges in data sharing, being an international public–private partnership conducted with participants from the PSEN1 E280A kindred, unique in that they are a more easily re-identified group, largely living in the Antioquia region in Colombia, sharing a single mutation and having more genetic homogeneity related to a founder effect,[20] and being a small group compared to the general population in Antioquia. Despite this challenge, the value of these important data in a special population with tremendous potential to inform the field warranted the robust development and implementation of a data-sharing strategy and process.

2 | METHODS

The API ADAD Trial was approved by the Ethics Committee at the Hospital Pablo Tobón Uribe and the regulatory authority in Colombia, Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA). Informed consent to participate in the trial and share anonymized data and samples was obtained from all study participants

TABLE 1 Baseline characteristics of PSEN1 E280A mutation carriers and non-carriers in the API ADAD Trial

Characteristic	Carriers	Non-carriers	*P*-value
Number	169	83	–
Age M ± SD	37 ± 6	43 ± 7	<0.001
Sex (n [%] female)	103 (61%)	57 (69%)	0.23
Education (years)	8.8 ± 4.0	8.2 ± 4.4	0.27
APOE ε4 carriers (*n* [%])	36 (21%)	19 (23%)	0.77
CDR global	0.05 ± 0.15	0.03 ± 0.12	0.23
CDR sum of boxes	0.15 ± 0.39	0.05 ± 0.17	0.03
FAST	1.12 ± 0.34	1.01 ± 0.11	0.006
Neuropsychiatric inventory	0.45 ± 1.66	0.37 ± 1.95	0.60
Geriatric Depression Scale	1.34 ± 1.82	1.18 ± 1.75	0.50
Florbetapir SUVRs M ± SD	1.13 ± 0.14	0.96 ± 0.04	<0.0001
Centiloids M ± SD	29.26 ± 24.75	−2.19 ± 8.23	<0.0001
1-3 microhemorrhages (*n* [%])	5 (3%)	6 (8%)	0.19

Abbreviations: API ADAD, Alzheimer's Prevention Initiative Autosomal-Dominant Alzheimer's Disease Rrial; *APOE*, apolipoprotein E; CDR, Clinical Dementia Rating; FAST, Functional Assessment Staging Test; PSEN1, presenilin 1; SD, standard deviation; SUVRs, standardized uptake value ratios.

RESEARCH IN CONTEXT

1. **Systematic review**: When the Alzheimer's Prevention Initiative Autosomal-Dominant Alzheimer's Disease (API ADAD) Trial was announced in 2012, it included a commitment to provide a public resource of data and biological samples after the trial is over. Leaders from API worked with those from other prevention trial programs and thought leaders to establish Collaboration for Alzheimer's Prevention (CAP) and its data and sample sharing principles; developed a strategy to share baseline data in ways that would protect participant confidentiality, genetic risk disclosure, and trial integrity; and reviewed information from the UK Anonymisation Network and relevant literature in PubMed to inform their decisions.
2. **Interpretation**: We report the availability of baseline data from the API ADAD Trial and describe the procedures needed to access data, protect research participant anonymity, and minimize the risk of disclosing a participant's ADAD mutation status.
3. **Future directions**: The trial was recently completed. Additional assays and analyses are in progress. Treatment data and samples will ultimately be shared with the research community in accordance with our original trial agreement and subsequently developed CAP principles. Baseline data and treatment data from mutation carriers and non-carriers in the trial promise to advance the detection, tracking, and study of preclinical Alzheimer's disease (AD); explore the impact of initiating treatment in carriers before or after biomarker evidence of amyloid beta plaque deposition; and inform the design, selection criteria, and endpoints in secondary and primary AD prevention trials.

and partners using policies and procedures that were informed by the Trial's Ethics and Cultural Sensitivities Committee[7] and performed in accordance with local, national, and international guidelines.

2.1 | Participant characteristics

To date, nearly 6000 7–75-year-olds members of the Colombian PSEN1 E280A kindred, including nearly 1200 mutation carriers, have been enrolled in the Colombian API Registry.[21] Two hundred fifty-two Registry participants who met our selection criteria[7] were enrolled in the trial, including 169 PSEN1 E280A mutation carriers who were randomized to crenezumab versus placebo and 83 non-carriers who were assigned to placebo. While baseline demographic, genetic, and clinical characteristics have been reported previously,[13] they are also presented in Table 1.

2.2 | API ADAD Trial design and measurements

The API ADAD Trial's design, inclusion and exclusion criteria; primary, secondary, and exploratory objectives; clinical, cognitive, biomarker, and assessment schedule were described previously.[7] All participants have had PSEN1 E280A and apolipoprotein E (*APOE*) genotyping, baseline and treatment florbetapir and fluorodeoxyglucose (FDG) positron emission tomography (PET) scans, magnetic resonance imaging (MRI), and collection of blood and DNA samples for future biomarker and genetic assessments. Biospecimens, related data, as well as treatment data, will be shared in accordance with the original agreement between Banner Alzheimer's Institute (BAI), API, and Genentech/Roche and subsequently developed CAP principles. A total of 130 participants had lumbar punctures for future cerebrospinal fluid (CSF) biomarker assessments. Genentech Tau Probe 1 (GTP1) PET scans for assessing tau tangle deposition were acquired in a subset of participants starting after randomization was completed, data from which will also be available in the same timeline as biospecimen and treatment data.

2.2.1 | Brain imaging

PET images were acquired on a Siemens/CTI Biograph mCT system and MRIs on a 3T Siemens Tim Trio system, all at the Hospital Pablo Tóbon Uribe in Medellin, Colombia. Image acquisition procedures have been described in detail.[18] Briefly, florbetapir PET scans were performed

using an intravenous (IV) bolus injection of ≈10 mCi of florbetapir, a 50 minute radiotracer uptake period, and a 20 minute dynamic emission scan. FDG PET scans were performed using an IV bolus injection of ≈5 mCi of FDG, a 30 minute radiotracer uptake period, and a dynamic 30 minute dynamic emission scan. Standard iterative algorithms were used to reconstruct images and correct for radiation attenuation and scatter.[18,19] GTP1 PET methods will be described when those data are reported and available. MRI pulse sequences were used to acquire a T1-weighted volumetric MRI, a T2-weighted fluid attenuated inversion recovery (FLAIR) image, a T2-weighted multi-echo gradient recalled echo (GRE) image, diffusion tensor image (DTI), a proton density-weighed image, and a resting state functional connectivity (fcMRI) image.

2.2.2 | Clinical and cognitive assessments

Five baseline cognitive assessments are compiled into a single measure, the API ADAD Composite Cognitive Test Score,[1] which includes: The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word list recall, Multilingual Naming Test, CERAD Constructional Praxis Test, Mini-Mental State Examination (MMSE; for orientation to time), and Raven's Progressive Matrices (subset).[7] Other cognitive assessments include the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Trail Making Test (TMT), and Free and Cued Selective Reminding Test (FCSRT).[7] Clinical scales assessed are the Functional Assessment Staging of Alzheimer's Disease (FAST) Scale, Geriatric Depression Scale (GDS), Neuropsychiatric Inventory (NPI), Clinical Dementia Rating Scale (CDR), and Subjective Memory Checklist.[7] Assessments were administered by psychometricians and qualified raters masked to all other study data.

2.3 | Data sharing plan

Because the API ADAD Trial recruited exclusively from the autosomal dominant AD kindred in Colombia the trial must adhere to country-specific data privacy regulations in addition to US standards for Food and Drug Administration–regulated clinical trials as required by NIA-awarded federal grants. Though the API ADAD Trial is conducted outside the United States, international regulations such as the General Data Protection Regulation (GDPR; Regulation [EU] 2016/679) do not apply to data shared from Colombia residents. GDPR-style principles such as legitimate interest as a basis for legal processing of personal data without informed consent does not apply in Colombia. Instead, the Colombia Data Protection Law (DPL) provides the rules for data controllers and processors of data collected from Colombian residents. Colombia's material regulations regarding use of personal data, including sharing data for scientific purposes, are primarily focused on informed consent, requiring consent of the intended and potential uses of the data collected. Blanket consents or opt-out mechanisms are not considered valid mechanisms for using personal data of Colombians because such methods do not reflect an express decision that can evidence the data subject's intention.

The trial's leadership and data-sharing teams consulted guidelines for regulatory authorities, comprehensive academic frameworks,[22] and other successful data-sharing programs.[9-12] Because the paradigm for sharing baseline data in a potentially label-enabling clinical trial had not yet been established, we vetted data-sharing approaches that would minimize risks to research participant anonymity and confidentiality, and clinical trial integrity by reviewing UK Anonymisation Network (UKAN) data-sharing policies and vetting strategies used by DIAN[11] to share observational data, baseline data from the DIAN-Trials Unit (DIAN-TU),[12] and screening data from the A4 Trial.[10] In addition to protecting anonymity, confidentiality, trial integrity, and the chance for regulatory approval, data-sharing policy development also aimed to recognize the work done to generate the data, and share data in transparent, fair, and inclusive ways.

The combination of the unique localization of hereditary, autosomal dominant carriers of an AD causative mutation with the fact that the trial was ongoing introduces the possibility of rare risks or threats to the trial participants. The API ADAD Trial team pressure-tested potential threats by identifying and assessing the deliberate and inadvertent risks of re-identification of participants, security breaches, and characterizing potential attack scenarios by parties acting as adversaries. A maximalist approach to clinical trial data sharing assumes that the at-risk population for re-identification is all patients in the country and has been used to anonymize other public data releases as it retains the highest degree of data utility post-anonymization. This approach is too broad for the API ADAD Trial, which draws from a single geographic region that is publicly recognized for its unique concentration of autosomal dominant AD.[14,15] However, the most conservative approach assumed that the at-risk population is all patients in the trial and resulted in widespread suppression of clinically relevant variables in the data and, in practice, would severely limit the scientific utility of novel investigations.

The API ADAD Trial balanced these approaches by considering real-world precedents in combination with reasonable assumptions about possible adversary knowledge. An adversary knowing who participated in a specific trial before accessing the data was deemed an unlikely scenario and would result in suppressing data to a level that prevented meaningful analysis. A real-world adversary knowing that a participant enrolled in one of several trials for a given indication over a particular period but does not know who is in the shared data from the API ADAD Trial is much more plausible.[22]

The API ADAD Trial further mitigated risk by restricting the number and the roles of those with access to sensitive data. Only a small subset of the BAI data managers involved in transferring data to approved researchers have access to the genetic information and are firewalled from all other team members and analysts. Making analysis results from data shared with approved researchers publicly available introduces the possibility of inadvertently unblinding a single trial participant or trial staff.

The API ADAD Trial will approve qualified researchers who agree to receive the data with reasonable stipulations integral to pragmatic, successful data sharing. Approved researchers become data recipients upon execution of data use agreements with the data provider, BAI, binding them to terms protecting trial participants, trial integrity, and

TABLE 2 Rules to reduce the risk of participant identification in the API ADAD Trial

Variable	Identifier type	Rule	Rule description
Subject ID	Direct	Scramble	Replace with random value
Age	Indirect	Replace	Derive new value to keep integrity (group age into categories). In addition, to avoid inferring individual mutation status via frequency tables, for example, via ranges, the data have been "age matched." Data from a small number of patients at age extremes have been removed so that the ranges across the two mutation status groups match.
Education level	Indirect	Review	Redact if not required for analyses; bin if required
Handedness	Indirect	Keep	No action taken
Country	Indirect	Keep	No action taken
Race	Indirect	Recode	Assign CDISC values for RACE
Ethnicity	Indirect	Review	Redact if not required for analyses
Sex	Indirect	Review	Redact if not required for analyses
BMI	Indirect	Review	Redact if not required for analyses; bin if required
Diabetes status	Indirect	Keep	No action taken
Smoking status	Indirect	Keep	No action taken
Concomitant medications	Indirect	Review	Retain coded terms, redact verbatim terms
Visit date	Indirect	Drop	Redact all dates (all baseline time point)
APOE genotype[a]	Sensitive	Keep	No action taken
PSEN1 genotype[a]	Sensitive	Keep	No action taken

Note: The table lists the suppression and masking decisions of specific direct and indirect identifiers of relevant variables in the API ADAD Trial.
Abbreviations: API ADAD, Alzheimer's Prevention Initiative Autosomal-Dominant Alzheimer's Disease Trial; *APOE*, apolipoprotein E; BMI, body mass index; CDISC, Clinical Data Interchange Standards; ID, identification; PSEN1, presenilin 1.
[a]These are highly sensitive variables but must be retained because they are a key analysis variable.

data compliance practices enforceable by law. We present an outline with specific principles used for risk reduction and mitigation for data-sharing purposes that a recipient must agree to in the data-sharing process in Figure 1.

Available data have been matched for age range to protect participant confidentiality and this allows researchers to request access to deidentified participant-level baseline and brain imaging data. Anonymization of shared data considers if a requested variable in the approved data subset does or does not meet the three criteria for direct or indirect identifiers. Direct identifiers are requested variables that are replicable, distinguishable, and knowable as singularly identifying of a trial participant (e.g., name or subject identification). Indirect identifiers are variables that may be replicable or knowable but do not distinguish unique participants and are analytically meaningful (e.g., age). Suppression and masking of available variables classified of direct and indirect identifiers are shown in Table 2.

3 | RESULTS

3.1 | Available data

Baseline trial data are available including demographic information; basic laboratory studies; vital signs; electrocardiograms; PSEN1 E280A and *APOE* test results; and the previously noted florbetapir PET, FDG PET, MRI images, florbetapir standardized uptake value ratios (and corresponding centiloids), API ADAD Composite, clinical ratings, and other cognitive test scores. Additional data, CSF, blood, and DNA samples from the participants' baseline and follow-up visits will become available in accordance with CAP principles, specifically that emerging data from ongoing trials should be made available as soon as possible with the intention of accelerating progress in the field through timely access, in this instance the earlier of either regulatory approval of crenezumab or 18 months. While timely access is the ideal, CAP acknowledges that maximal and timely access may be constrained by the need to maintain blinding and confidentiality.[8] Adopting CAP principles incentivized the API ADAD Trial to assess novel risks and liabilities unique to sharing data from an ongoing clinical trial.

3.2 | Data requests, requirements, and additional risk mitigation procedures

The API ADAD Trial employs a controlled release approach for human research participant data, consistent with the recommendations of the NIA and other experts. Accordingly, the specific procedures and policies for this data set require vetting researchers requesting access to clinical trial data and places them under a data use agreement in alignment with these principles. BAI and Roche are committed to maximizing shareable data and will update existing processes and policies

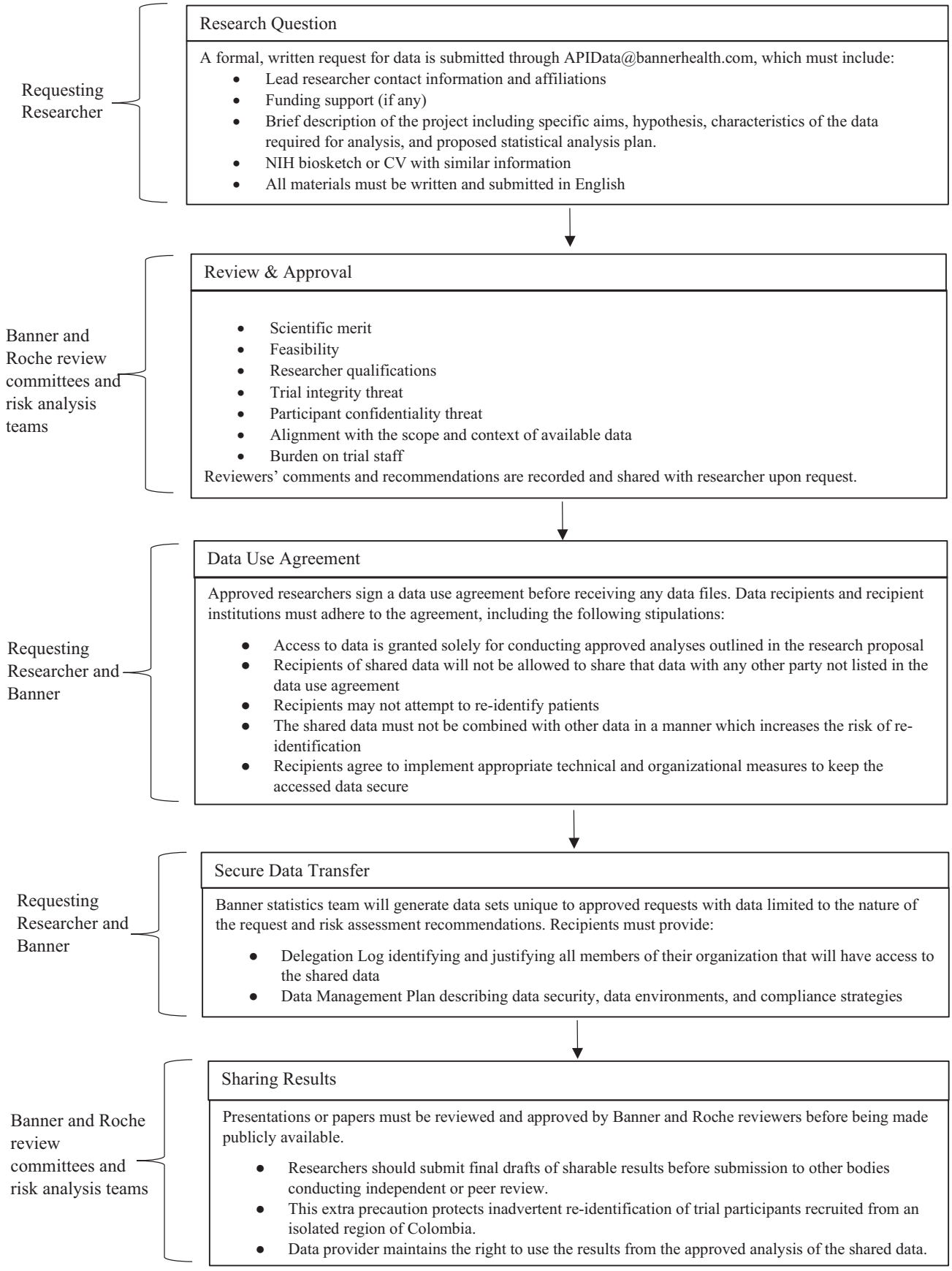

FIGURE 1 Alzheimer's Prevention Initiative Autosomal-Dominant Alzheimer's Disease (API ADAD) Trial baseline data-sharing process and data recipient requirements. CV, curriculum vitae; NIH, National Institutes of Health

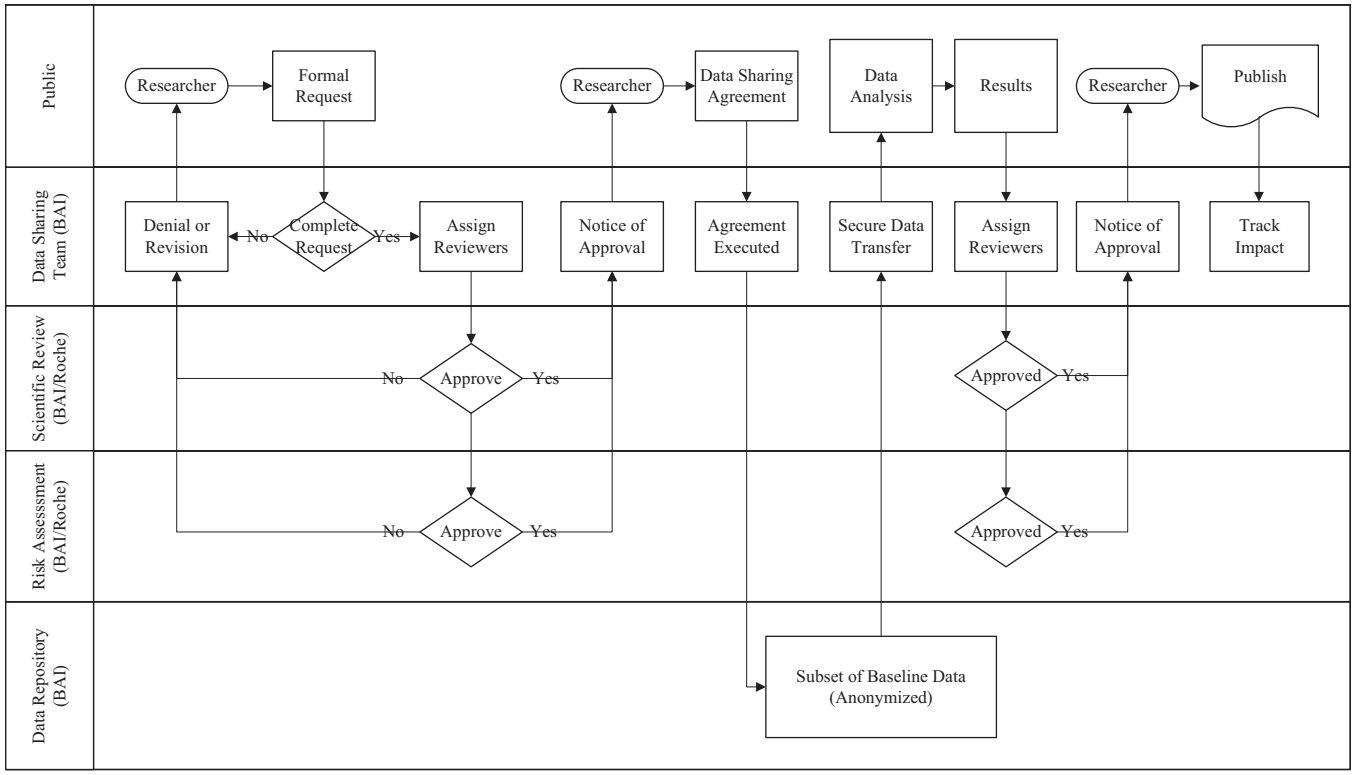

FIGURE 2 API ADAD Trial baseline data request, review, a approval, transfer, analysis, and publishing process. This process map offers a visual representation of the cycle a formal request follows for request, review, approval, transfer, analysis, and publishing. Steps are also categorized and visualized to illustrate what tasks are performed by which members of the multi-stakeholder collaboration that is required for public sharing of a public-private Food and Drug Administration–regulated clinical trial data and imaging. BAI, Banner Alzheimer's Institute

as best practices for data sharing evolve over time. The current process for researchers to access baseline data from the API ADAD Trial, subject to all applicable data and privacy laws, is outlined in Figure 1.

If the request is denied, the researcher will be provided a brief explanation, copies of the reviews, and an opportunity to revise and resubmit a request. Figure 2 illustrates the comprehensive process cycle of a formal request including review, approval, analysis, results, and publishing. If ambiguity arises at any step in the process, or if a reviewer believes it would help to communicate with a researcher about the scientific approach or statistical analysis plan, the trial data sharing team can schedule a meeting with the researchers making the request. The API website hosts additional materials and details regarding the API ADAD Trial and data-sharing process for review or download at https://alzheimerspreventioninitiative.com.

4 | DISCUSSION

Baseline data from cognitively unimpaired PSEN1 E280A mutation carriers and non-carriers in the API ADAD Trial are available to the public. Our baseline data-sharing program is intended to advance the study of preclinical AD, anticipate the sharing of additional data and biological samples from follow-up visits, and underscore the importance of data sharing in all trials.

Baseline trial data from the cognitively unimpaired mutation carriers and non-carriers from the world's largest ADAD kindred will provide an invaluable scientific resource for the field. The mutation carriers are virtually certain to develop AD and were assessed starting within 15 years of their median age of MCI onset (44 years old).[16] Data from this extremely well-characterized homogeneous population (i.e., carriers with a single ADAD mutation, carriers and non-carriers from the same kindred, all Spanish-speaking, in the same general location, and assessed at a single site) have the potential to support the detection, tracking, and study of preclinical AD, and the evaluation of promising treatments with increased statistical power. These data will complement other observational API[2,4,5] and COLBOS[15,23] studies in the Colombian PSEN1 E280A kindred; observational and trial data from persons with different ADAD mutations (including DIAN and other ADAD cohorts); and cohorts involved in the preclinical detection, tracking, and study of sporadic AD. Baseline data will provide an opportunity to compare brain imaging, cognitive assessments, clinical data, and their relationships in mutation carriers and non-carriers. Additionally, they will afford the ability to explore the value of new analytic techniques, and to set the stage for using longitudinal data and biospecimens (including CSF, blood-based biomarkers, tau PET scans, and DNA samples) from crenezumab-treated mutation carriers, placebo-treated mutation carriers, and placebo-treated non-carriers. Analyses of the data will help determine the diagnostic, prognostic, and

potentially theragnostic role of promising biomarkers in cognitively unimpaired persons at genetic and biomarker risk for AD, an opportunity all researchers in the field, not just those affiliated with API ADAD Trial, should have.

Unpublished data from the trial indicates that more than half of the mutation carriers in the trial did not yet meet PET criteria for the presence of at least moderately frequent neuritic Aβ plaques and about one third did not yet have PET evidence of any neuritic Aβ plaques at the time of investigational treatment initiation, providing a chance to explore the differential effects of crenezumab treatment in the primary versus secondary prevention of preclinical ADAD. With public availability, these data can help inform the field, with important implications in this instance, for primary (absence of Aβ) versus secondary (presence of Aβ but asymptomatic) prevention trials.

The Colombian PSEN1 E280A kindred introduces special challenges in data and sample sharing. When the trial began, most cognitively unimpaired kindred members did not want disclosure of their ADAD mutation status to be a requisite for enrollment leading us to include mutation carriers and non-carriers from the same kindred.[7] Additionally, because information about a participant's carrier status could potentially influence cognitive performance and researchers' clinical assessments, special efforts are needed to share data in such a way as to not inadvertently disclose genetic status and ensure that participants and research raters remain blinded to this information.

The data that can be shared have several limitations. Tau PET scans were not introduced until enrollment was completed, and CSF, blood, and DNA samples will not become available until a later date. While many mutation carriers did not have PET evidence of Aβ plaque deposition, we and others have demonstrated earlier evidence of (what is thought to be primarily diffuse) Aβ plaques prior to PET positivity,[24] including in Colombian PSEN1 E280A mutation carriers.[17] The full value of this resource will not become apparent until additional data and biological samples become available.

The API ADAD Trial baseline data-sharing program is intended to advance the study of preclinical AD, set the stage for the analysis of data from the entire trial, and underscore the importance of data sharing in all trials. Because there is much to learn about the optimal ways to share trial data, our data sharing program may evolve over time .

ACKNOWLEDGMENTS

This paper was made possible by Grants RF1AG041705, R01AG055444, and P30AG072980 from the National Institute on Aging (NIA). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH/NIA. The API ADAD Trial is a public–private partnership led by researchers from Banner Alzheimer's Institute, the Grupo Neurociencias de Antioquia (GNA; part of the University of Antioquia and the main study site for the API ADAD Trial), Genentech/Roche, and the NIA. The API ADAD Trial is supported by the above mentioned NIA grants, Genentech and its parent organization Roche, and generous philanthropic contributions to the Banner Alzheimer's Foundation. The API ADAD Trial and its related programs have been supported by Banner Alzheimer's Foundation, NOMIS Foundation, FIL/Fidelity Bermuda Foundation, Flinn Foundation, and Colciencias. The authors would like to thank their valued research participants and families; current and former colleagues in the API ADAD Trial; and our collaborators from DIAN, the A4 Trials Program, and CAP for exchanging information about policies and procedures to share data and samples in ways that provide appropriate participant and trial protections.

CONFLICTS OF INTEREST

Dr. Reiman reports grants from the NIA (RF1AG041705, R01AG05544, P30AG19610, P30AG072980), Banner Alzheimer's Foundation, and the NOMIS Foundation and is a scientific advisor to Alzheon, Aural Analytics, Denali, Green Valley, Retromer Therapeutics, and Vaxxinity. He has research agreements with Genentech/Roche and Avid/Lilly. He is the co-founder, advisor, and shareholder in ALZPath. Dr. Pruzin receives research support from the Alzheimer's Association (AACSF-20-685828), The State of Arizona (Arizona Alzheimer's Consortium), and The Banner Health Foundation. Drs. Lopera, Rios-Romenets, Giraldo, Acosta-Baena, and Tobon report participation in other projects financed by the National Institutes of Health, Comité para el Desarrollo de la Investigación, and COLCIENCIAS. Dr. Quiroz reports grants from the NIH Office of the Director (DP5OD019833), the NIHNIA (R01AG054671), the Alzheimer's Association, and Massachusetts General Hospital ECOR. Dr. Langbaum reports grants from NIA (RF1AG041705-01A1, P30AG072980, R01AG05544) and received consulting fees from Alector, Biogen, Denovo Biopharma, and Provoc. Banner Health has received research support from Genentech/Roche, Banner Alzheimer's Foundation, FIL, Nomis Foundation, and the State of Arizona (Arizona Alzheimer's Consortium). Dr. Thomas has received consulting fees from Toyama, Avraham, Intel-Genx, and Biogen. He has received research support from the National Institute on Aging. Dr. Chen is supported by grants from the National Institute on Aging (RF1AG041705, R01AG05544, P30AG19610, P30AG072980) and is a paid consultant to Green Valley Pharmaceutical, Shanghai China; is an adjunct Professor at Beijing Normal University, China; and a paid consultant of Prothena, CA. Dr. Su was supported by NIH grants R01AG031581, R01AG069453, P30AG019610, R01AG055444, R01AG058468, U19AG024904, R42AG053149, R21AG065942, Alzheimer's Association AARG17532945, BrightFocus Foundation ADR A2017272S, and Arizona Department of Health Services (ADHS) and the State of Arizona, ADHS Grant No. CTR040636. Drs. Hu and Sink are full-time employees of Genentech, Inc., a member of the Roche Group and own stock in Roche. Dr. Tariot reports grants from the NIA (RF1 AG041705-01A1, R01 AG055444,1R01AG058468) and received consulting fees from AbbVie, AC Immune, Acadia, Axsome, Biogen, BioXcel, Cortexyme, Eisai, Genentech, Otsuka & Astex, Merck & Co., Novo Nordisk, Syneos, and T3D Therapeutics. Until 2020, he owned shares in Adamas Pharmaceuticals. Banner Health has received research support from Genentech/Roche, Novartis, Eli Lilly & Co., Banner Alzheimer's Foundation, FIL, Nomis Foundation, and the State of Arizona (Arizona Alzheimer's Consortium). He is a contributor to a patent owned by the University of Rochester, U.S. Patent # 11/632,747, "Biomarkers of Neurodegenerative disease." The authors

report no further potential conflicts of interest. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Reiman EM, Pruzin JJ, Rios-Romenets S, et al. A public resource of baseline data from the Alzheimer's Prevention Initiative Autosomal-Dominant Alzheimer's Disease Trial. *Alzheimer's Dement*. 2022;1-9. https://doi.org/10.1002/alz.12843