Positive Emotion Regulation Intervention for Benzodiazepine Receptor Agonist Deprescribing in Older Adults: Anxiety Lowering and Deprescribing Through Emotion Regulation (ALDER)

NCT06359314

Statistical Analysis

Demographic and clinical characteristics were summarized using descriptive statistics to characterize the sample (e.g., means and standard deviations or medians and IQR when required by the distribution; counts and percentages). Pre- to post-intervention changes in patient-reported outcomes were assessed for the sub-sample of participants who completed follow-up surveys. Change in days per week of medication use was assessed using Wilcoxon's exact tests. Changes in PROMIS measures were assessed using Wilcoxon's exact tests.

STUDY TITLE: Positive emotion regulation intervention for benzodiazepine receptor agonist deprescribing in older adults: Anxiety Lowering and Deprescribing through Emotion Regulation (ALDER)

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VERSION DATE:
4/5/2024

FEDERAL FUNDING:

Funding Agency:	NIH	
Sponsored Research ID#:	FP00001624	
Does the grant indicate that covered activities will include Human Research? (Yes / No / Unknown)	Yes	
	Institution Name:	Human Research Assessment *** Non-Exempt Human Research
Prime Award Recipient*	Northern California Institute for Research and Education	
Sub-Award Recipients**	Northwestern University	

* The prime award recipient is always engaged in Human Research and must have IRB oversight when one or more sub-award recipients conduct non-exempt Human Research.
Many federal agencies require that when more than one domestic site engages in non-exempt Human Research, all sites must rely on the review of one "Single IRB." If this applies to your study, you must obtain a Single IRB Letter of Support and IRB Fee Quote from the Northwestern University IRB Office before the Northwestern University IRB will review your study. Submit a Single IRB Consultation Request to initiate this process.

***Include the activities of all non-Northwestern affiliated sites in the multi-site/collaborative research section of the protocol below.*

****The federal funding application should include plans for whether award recipients will engage in Human Research. Based on the funding application, provide an assessment of the activities at each site and update the table if the planned activities change or if another IRB reviews the activities and makes a different determination.*

RELATED STUDIES:
N/A

Check any **applicable** boxes in the table below – you will be asked for further detail on these topics later in the protocol form:

Indicate Vulnerable Populations to be enrolled: ☐ Children ☐ Cognitively Impaired Adults ☐ Pregnant Women (IF the research activities will affect the pregnancy or the fetus) ☐ Prisoners (or other detained/paroled individuals)
☐ International Research (check this box if you will collect data from individuals located outside the United States)
☐ Research involving external collaborators (some research activities will be carried out by individuals not employed by Northwestern or NU affiliates will carry out some research activities)
☒ Research has U.S. Federal government funding via one or more direct awards or a sub-award (e.g., NIH, NSF, other federal agencies or departments)

1.0 Purpose and rationale of the study:

Deprescribing benzodiazepine receptor agonists, particularly for older adults, is a key public health goal. Benzodiazepine receptor agonists (BZRAs) are prescribed frequently to people with anxiety and sleep disturbances, many of whom have comorbid depression.[1,2] Although these medications can alleviate symptoms in the short term, for many patients, the risks of long-term use outweigh their benefits.[1-3] BZRA use is especially risky for older adults, due to high levels of comorbidities, polypharmacy and drug-drug interactions, along with age-related changes in pharmacodynamics and pharmacokinetics.[2-8] Even as deprescribing programs have grown, the proportion of BZRA prescriptions going to older adults has increased.[9] Lack of mental health resources is a primary barrier to deprescribing BZRAs to older adults in primary care.[10] Therefore, interventions that can alleviate anxiety and sleep disturbances are important complements to BZRA deprescribing.[11]

Positive emotion regulation is a novel, efficacious approach to maintaining health and well-being. In this study, we will tailor and pilot a non-pharmacologic integrative health intervention, ALDER (Anxiety Lowering and Deprescribing through Emotion Regulation), that specifically targets positive emotion. Research has shown that positive emotions, independent of negative emotions, are uniquely related to a host of adaptive psychological and physical health outcomes,[12-19] such as improved cognitive function,[20-22] better relationships and mental health,[23] better physical health,[24] and even a lower risk of mortality.[25-29] These effects are true for older adults as well.[30-32] Thus, a growing body of evidence suggests that targeting the ability to experience and maintain positive emotion is a promising approach to promoting physical and psychological adjustment.[15,33,34]

Building on this body of research, our team developed a multicomponent intervention that focuses on skills for increasing positive emotions.[35-37] Previous trials demonstrated feasibility, acceptability, and efficacy in different clinical populations and settings; outcomes include increased positive affect and meaning and purpose, decreased anxiety, depression and social isolation, improved adherence to reduced substance use, and other aspects of well-being.[37-48] The online, self-guided intervention teaches 8 empirically-supported behavioral and cognitive skills over 5 weeks (see Table 1), each of which includes 1-2 days of didactic material and 5-6 days of skills practice; each day's effort takes approximately 10-15 minutes.[37,48] We hypothesize that older adults enrolled in ALDER will experience increased positive emotions and decreased distress, anxiety and sleep disturbance, which may increase success of BZRA deprescribing in patients who decide, within the course of their ongoing clinical care, to consider reducing or gradually stopping use of BRZA.

Accordingly, **our aims are to**:

(1) **Tailor ALDER for implementation as an adjunct to BZRA deprescribing for older adults receiving primary care at NM**. We will conduct key informant interviews and/or focus groups with n=20 older adults who are identified as candidates for BRZA deprescribing and with n=20 clinicians who provide primary care for older adults prescribed BZRAs. Results will inform intervention tailoring and selection of implementation strategies for use in Aim 2.

(2) **Evaluate feasibility, acceptability, and adoption of ALDER among older adults who are candidates for BZRA deprescribing**. We will enroll n=40 patients through primary care clinics and deliver ALDER in a self-guided, online format. Assessments will be administered at baseline and post-intervention, including measures of engagement and retention, deprescribing attitudes and patient-reported outcomes such as anxiety, sleep, and positive affect.

(3) **Design a type 2 hybrid implementation-effectiveness trial based on stakeholder feedback**, including follow-up interviews with patients who participated in the Aim 2 trial, as well as their clinicians.

As a multi-component intervention, ALDER has the potential to be more effective than interventions that focus on a single skill (See Table 1).[49,50] Our web-based approach has the advantages of low cost, easy dissemination, and accessibility, resulting in a scalable program that could be delivered to a limitless number of older adults across multiple, diverse sites in the future. Our interdisciplinary, stakeholder-engaged team therefore will leverage the results of the proposed tailoring and pilot project to generate a hybrid implementation-effectiveness trial. Thus, the current ALDER proposal is the first step towards our ultimate goal of developing and evaluating interventions that effectively enable BZRA deprescribing, improving safety, health, and well-being for older adults.

Table 1. Overview of ALDER intervention

Week	Skills	Goals	Practice Exercises
1	**Positive Events, Savoring, and Gratitude**	Recognize positive events and associated positive emotions; practice amplifying the experience of positive events; learn to practice gratitude	Note a positive event each day and write about it (savoring); start a daily gratitude journal
2	**Mindfulness**	Learn and practice the awareness and nonjudgment components of mindfulness	Daily informal mindfulness activities and 10-minute formal breath awareness activity
3	**Positive Reappraisal**	Understand positive reappraisal & how it can lead to increased positive emotions in the face of stress	Report a relatively minor stressor each day, then list ways it can be positively reappraised
4	**Personal Strengths, Attainable Goals**	Recognize personal strengths, skills, or talents; Understand benefits of goals that are appropriately challenging but still feasible	List a strength each day and how it was "expressed" behaviorally; work toward an attainable goal and note progress each day
5	**Self-Compassion**	Learn benefits of being kind toward oneself, even when under stress	Practice changing harsh self-criticism to self-compassion

2.0 Enrollment Criteria (who can be in your study and who would not be eligible to participate in your study):

Aim 1: Interviews and/or Focus Groups

- Clinicians' eligibility criteria are:
  a) ≥50% effort in clinical care.
  b) Prescribed BZRAs to ≥20 older adults in the past year.

c) Have access to a computer, tablet, phone, or other device that can be used to join a virtual focus group or interview.

- Patients' eligibility criteria are:
  a) Age ≥65
  b) BZRA prescribed via NM primary care.
  c) Able to read and speak in English. All ALDER study materials (screeners, consent form, ALDER intervention prototype, etc.) will be available only in English and all interviews and focus groups will be conducted in English.
  d) Not diagnosed with dementia.
  e) Access to a computer, tablet, phone, or other device that can be used to join a virtual focus group or interview.

Aim 2: Single-arm Pilot Trial

- Initial eligibility criteria:
  a) Age ≥65
  b) ≥1 NM Internal Medicine clinic visits within past year.
  c) BZRA prescribed by NM primary care within the past 1 year.
  d) Exclusion: enrollment in Hospice, dementia diagnosis, seizure diagnosis, REM sleep disorder diagnosis.

- Additional self-reported eligibility criteria will be:
  a) Take BZRA at least twice a week.
  b) Daily access to internet-connected device, as ALDER is an online intervention.
  c) Ability to read and speak in English. All ALDER study materials and communication (screeners, consent, ALDER intervention, etc.) will be available only in English.

- Patients who participated in the Aim 1 focus groups will be able to participate in the Aim 2 trial as long as they meet the above enrollment criteria.

Aim 3: Interviews

- Clinicians' eligibility criteria are:
  a) Staff at healthcare clinics where Aim 2 participants receive healthcare. It is not a requirement for staff to be involved in the treatment of patients who participated in Aim 2.
  b) Have access to a computer, tablet, phone, or other device that can be used to join a virtual interview.
  c) Willing to consent to audio recording of interview
- Patients' eligibility criteria are:
  a) Participated in the Arm 2 pilot trial
  b) Have access to a computer, tablet, phone, or other device that can be used to join a virtual interview.
  c) Willing to consent to audio recording of interview

3.0 Sample Size:

Aim 1: Interviews and/or Focus Groups

- **Total= up to 40 participants**
  - Up to n=20 NM clinicians
  - Up to n=20 older adults who are candidates for BZRA deprescribing

Aim 2: Single-arm Pilot Trial

- Up to n=40 older adults who are candidates for BZRA deprescribing

Aim 3: Interviews

- Total= up to 60
  - Up to n=40 Aim 2 pilot participants
  - Up to n=20 clinic staff

Sample size for Aims 1 and 3 are based on expected numbers required to reach saturation in qualitative data collection. Aim 2 sample size is designed to estimate feasibility, acceptability, and adoption of the intervention – rather than its efficacy. Nonetheless a sample size of n=40 in Aim 2 will allow us to estimate 95% confidence intervals (CIs) for post-intervention measures with some precision (around means within SD 0.31; proportions within SD 15.5%), even with 20% attrition (means within SD 0.35; proportions within SD 17.3%).

4.0 Recruitment and Screening Methods:

Aim 1: Interviews and/or Focus Groups

Clinician interviews/focus groups: We will be contacting NM clinicians who prescribe BZRAs through email, sent out by a member of the ALDER Study Team. **Please see Aim 1 clinician email template.** We will recruit clinicians via relationships established through (but not limited to) Northwestern Medicine and affiliated networks. Interested clinicians will respond to the email requesting information on how to participate, and/or provide referrals to other BZRA prescribing clinicians who they feel may be interested in helping tailor the intervention. Respondents will complete a brief REDCap screening form to confirm eligibility. An IRB-approved study team member will respond to clinicians with scheduling details, etc. Since the purpose of the clinician interviews/focus groups is to tailor the intervention for older adults who are candidates for BZRA deprescribing and these clinicians are not directly participating in the intervention itself, the online agreement to participate will be recorded through REDCap prior to receiving the intervention content for review. Registered participants will receive a consent document and secure videoconferencing link, along with a prototype of ALDER to review.

Patient interviews/focus groups: Potentially eligible older adults will be identified via Northwestern's Enterprise Data Warehouse (EDW), recruitment research databases (i.e., Research Match, etc.), or direct invitation from Northwestern clinical staff and invited via email to complete eligibility screening via a screening survey in REDCap and/or telephone screening. **Please see Aim 1 patient email template.** If patients are found to be eligible, an IRB-approved study team member will respond to them with scheduling details, etc. Scheduled participants will receive a consent document to sign through REDCap and a secure videoconferencing link, along with a prototype of ALDER to review. If an individual does not meet the criteria, they will see a message after completing the REDCap pre-screener that thanks

them for their time, but notifies them that unfortunately, they are ineligible to participate in the ALDER study.

Aim 2: Single-arm Pilot Trial
Northwestern's EDW will provide lists of patients meeting initial eligibility criteria. Research Match and other similar research recruitment databases, along with direct referral from healthcare staff/clinicians, may also be used to increase enrollment. (For example, clinicians may review their clinic schedules and notify us of any patients with whom they have recently discussed BRZA deprescribing. In those cases, the study team would still complete eligibility screening and informed consent with patients, according to our standard enrollment processes. Patients will be free to decline participation in ALDER, and that would not impact their ability to freely decide whether and how to undergo BRZA deprescribing, which will remain within the context of their existing healthcare relationship with their prescribing clinician, regardless of their enrollment status in this research study.) Patients meeting initial criteria will receive an email introducing the study and inviting them to complete eligibility screening in REDCap. **Please see Aim 2 patient email template and eligibility screening form.** These questions verify whether an individual has met all study criteria to participate. Eligible patients will be able to consent via REDCap or to ask study questions by telephone. If an individual does not meet the criteria, they will see a message after completing the pre-screener that thanks them for their time, but notifies them that unfortunately, they are ineligible to participate in the ALDER study.

Data collected from the pre-screener link will be stored on a secure, HIPAA-compliant, and password-protected server at the Feinberg School of Medicine. We will flag identifiers on the REDCap platform, so that these variables will be excluded from any data exports. For example, we will flag First Name, Last Name, phone number, and email address. Any data from the pre-screener will only be for purposes of gauging the reach of our recruitment efforts such as zip code and assessing trends or characteristics among those who take the screener. Outside of REDCap, identifying information will never be linked with the data from the pre-screener. Only de-identified data will be exported from REDCap and saved on the password-protected FSM server. Only IRB-approved individuals will be able to access the data on REDCap. This de-identified data will be aggregated and used only for the purposes of gauging recruitment trends.

Aim 3: Interviews
The Aim 2 consent form will include an optional question asking patients if they are willing to participate in a post-intervention follow-up interview. If they agree, they will be contacted after the trial is over to schedule a feedback interview. **Please see Aim 3 patient email template**. Additionally, we will recruit clinic staff by email, inviting them to participate in a follow-up interview to obtain their feedback on the trial. **Please see Aim 3 clinician email template**. These Aim 3 qualitative data will be used to design future studies, such as fully-powered efficacy and implementation trials of ALDER.

5.0 Research Locations:

Northwestern University in Chicago, IL is the main research location, and we are relying on a single IRB via Northwestern. All study procedures can be conducted remotely, allowing us to enroll

stakeholders and pilot participants receiving or delivering care across the range of NM clinical settings (e.g., urban Chicago, suburban Illinois). Northwestern University will be conducting all study procedures; the University of California at San Francisco, the prime award recipient, will not be involved in any research activities. The research employs the web hosting services of BrightOutcome (https://www.brightoutcome.com/), a company experienced in building and hosting online platforms for patient reported outcomes research. Once we have tailored the intervention content in Aim 1, study staff will load the ALDER content into BrightOutcome's web-hosting pages. BrightOutcome is not involved in the study design, nor will they use data collected in any phase of this project. Drs. Addington and Moskowitz have successfully partnered with BrightOutcome to build and host websites for numerous positive emotion intervention projects. BrightOutcome also has a proven track record of collaboration and delivery of technology products/services to investigators at the Feinberg School of Medicine.

6.0 Multi-Site or Collaborative Research:

All study procedures will take place at Northwestern University. However, because Northwestern is a sub-award recipient, ALDER is classified as a collaborative study. We will be pursuing a reliance agreement with the prime award recipient, the University of California at San Francisco, through SMART IRB with Northwestern's IRB serving as the IRB of Record. The appropriate documentation will be uploaded to eIRB when the reliance agreement has been executed. No activities will happen at relying sites until reliance agreements are fully executed and appropriate local regulatory processes are followed.

7.0 International Research (where data collection will occur outside the United States and U.S. territories, including online activities)

N/A

8.0 Procedures Involved:

Please check the boxes for all applicable data collection procedures you plan to use:

☒ One-on-one interviews

☒ Focus Groups

☒ Questionnaires/surveys

☒ Secondary Data Analysis (medical record data, educational records, government or private sector datasets, etc.)

☐ Ethnographic observation

☐ Physiological measurements (e.g., EEG, EKG, MRI)

☐ Biospecimen collection (saliva samples, blood draws, hair samples, etc.)

☐ Mobile applications/data collection devices (e.g., Fitbits, actigraphs, etc.)

☐ Behavioral decision making tasks (e.g., puzzles, interactive games, etc.)

☐ Physical activities such as walking and other forms of exercise

☐ Other procedures (briefly list types of procedures here if not covered by the check-boxes above):

Aim 1: Interviews and/or Focus Groups

If an eligible individual agrees to participate in a focus group or interview, they will receive a consent document and secure videoconferencing link, along with a prototype of ALDER to review. Consistent with qualitative and pilot research guidelines,[51,52] semi-structured discussion guides will be designed to evaluate feasibility, attitudes, and preferences regarding ALDER content and delivery, and barriers and facilitators to implementing ALDER. Questions will assess: 1) attitudes towards BZRA deprescribing and programs like ALDER; 2) suggestions for tailoring ALDER content and maximizing engagement; and 3) recommendations for enrolling patients in ALDER, specifically how best to reach and retain a diverse group of older adults while maximizing clinic flow and quality and safety of care. The time commitment is estimated at up to an hour for interviews and 90 minutes for focus groups, and participants will receive $100 as compensation. Interviews will be audio recorded and transcribed in a de-identified manner.

Based on Aim 1 results and stakeholder input, we will modify ALDER and the Aim 2 design. We may revise the order of ALDER skills or terminology used to describe them, select photos that are representative of older adults' experiences, design practices that are relevant and engaging for this population, and update system features to ensure ALDER usability and adoption. In addition, we may adapt Aim 2 procedures, such as eligibility criteria, enrollment strategies, or outcome measures, to maximize feasibility and acceptability from the perspective of both patient and clinical stakeholders. In the case of any Aim 1 feedback that necessitates Aim 2 revisions, appropriate IRB approval will be obtained prior to initiating the updated Aim 2 procedures.

Aim 2: Single-arm Pilot Trial

Consent and Baseline

After the screening process, if the individual wants to continue, the PD or study staff member will email the individual a link to the online consent form through REDCap.

Consent scenarios:

- If a participant consents "Yes," they will automatically be directed to their online baseline assessment (T1) for completion.
- If an individual does not respond to the consent form, our study team will follow- up with a reminder up to 3 times by phone or email (based on information provided on the screener).
- If an individual responds "No" and declines to participate, they will see a message thanking them for their time and answer a brief (optional) question about why they declined.

Consented participants (up to n=40) will complete baseline assessments in REDCap. Assessments will take up to approximately 30 minutes to complete. ALDER staff will then create an ALDER account on the BrightOutcome platform for enrolled participants. Participants' study ID, first names, last initials, email addresses, and time zones will be entered into the ALDER online program hosted on BrightOutcome. Participants will then receive an invite email granting them access to ALDER on the mobile-responsive BrightOutcome platform, which can be used on any internet-connected device in any

location. ALDER teaches 8 empirically supported behavioral and cognitive skills over 5 weeks. Each week includes 1-2 days of didactic material estimated to take up to 1 hour to complete, and 5-6 days of daily home practice and emotion reporting estimated to take 10-15 minutes each day. Participants cannot skip ahead, but they can opt to return to old lessons or exercises. As in our previous mHealth trials,[44,48] participants will be asked to complete ALDER within 7 weeks to allow for varying schedules and self-pacing. In week 8, we will send the post-intervention assessment via REDCap; respondents will receive a $50 gift card. Data from the ALDER platform will provide objective usage metrics (see Measures). All data will be securely stored and accessible only to IRB-approved staff.

Table 1. Overview of ALDER intervention

Week	Skills	Goals	Practice Exercises
1	**Positive Events, Savoring, and Gratitude**	Recognize positive events and associated positive emotions; practice amplifying the experience of positive events; learn to practice gratitude	Note a positive event each day and write about it (savoring); start a daily gratitude journal
2	**Mindfulness**	Learn and practice the awareness and nonjudgment components of mindfulness	Daily informal mindfulness activities and 10-minute formal breath awareness activity
3	**Positive Reappraisal**	Understand positive reappraisal & how it can lead to increased positive emotions in the face of stress	Report a relatively minor stressor each day, then list ways it can be positively reappraised
4	**Personal Strengths, Attainable Goals**	Recognize personal strengths, skills, or talents; Understand benefits of goals that are appropriately challenging but still feasible	List a strength each day and how it was "expressed" behaviorally; work toward an attainable goal and note progress each day
5	**Self-Compassion**	Learn benefits of being kind toward oneself, even when under stress	Practice changing harsh self-criticism to self-compassion

Table 2. Timeline of ALDER Study

Aim 1 (Months 1-3)	Participant Population	# of Participants
Patient focus groups	Patients (over 65 y/o) who are prescribed a BZRA via NM primary care clinics*	Up to 20
Clinician interviews	Clinicians who have prescribed a BZRA to greater than 20 older adults in the past year*	Up to 20
Aim 2 (Months 3-9)		
Single-arm pilot trial	Patients (over 65 y/o) who are prescribed a BZRA via NM primary	Up to 40

	care clinics with two or more chronic conditions*	
Aim 3 (Months 9-12)		
Patient interviews	Aim 2 pilot trial participants*	Up to 40
Clinician interviews	Clinicians at healthcare clinics where Aim 2 participant receive healthcare*	Up to 20

*See Enrollment Criteria section for complete list of eligibility requirements.

Time commitment:
The estimated time commitment for ALDER (Aim 2) is up to 14 hours over 8 weeks.

Event	Time Commitment
2 surveys (up to 30 minutes each)	1 hour
5 ALDER Sessions	<5 hours
Daily Home Practice and emotion reporting	<8 hours
Total Hours	**<14 hours**

Measures:
Feasibility metrics will include enrollment rate (# consented/ # eligible) and retention rate (# of complete post-intervention assessments/ # consented). We will record the numbers of study invitations sent and of participants enrolled/month, and reasons for ineligibility and for declining participation.
Acceptability will be measured during REDCap post-intervention assessment with items used in prior research (e.g., Acceptability of Intervention Measure) to evaluate relevance of and satisfaction with interventions in implementation and pilot trials.[53-54]
Adoption will be assessed via usage metrics from the BrightOutcome platform (e.g., mean % of pages viewed, number of skills and practice exercises used). During post-intervention assessment, we also will ask participants to complete a checklist of reasons for non-adherence (e.g., not enough time, lost interest, forgot).
Patient-reported outcomes will be collected at baseline and post-intervention via REDCap, using the 4-item Perceived Stress Scale, along with PROMIS computer adaptive tests (CATs) of anxiety, positive affect, meaning and purpose, depression, and sleep disturbance. The Differential Emotions Scale (DES) will be administered daily throughout the ALDER intervention on the BrightOutcome website.[55-60]Demographics (e.g., gender, race, age) will be collected at baseline to characterize the sample and examine potential moderators.
BZRA usage, symptoms, and attitudes: Participants will self-report the name of BZRA(s) they use, frequency of use (# per week), and reasons for using (anxiety, sleep, stress, other). To measure attitudes towards BZRA use, we will also administer the revised Patients' Attitudes towards Deprescribing questionnaire for benzodiazepine receptor agonists (rPATD-BZRA). In accord with safety monitoring (see those sections below), we also will administer weekly the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ).
Clinical variables will be abstracted from the electronic health record via EDW reports. These will include rate of BZRA usage (total dose/days to refill, measured up to 3 months post-intervention), along with

covariates and adverse events (e.g., , medication list, falls, withdrawal). Participants will also complete the self-administered comorbidity questionnaire at baseline.

Aim 3: Interviews

We will conduct follow-up interviews with Aim 2 pilot participants (up to n=40 older adults) and with up to 20 clinic staff who provide care to patients who take BZRAs. Interview procedures will be like those in Aim 1 (e.g., conducted remotely, de-identified transcripts, $100 compensation). Semi-structured

interview guides will be designed to elicit what went well in Aim 2 and recommended changes for future iterations of ALDER. Questions will assess: 1) facilitators and barriers to enrollment and adherence; 2) perceived benefits and drawbacks of implementing (for clinic staff) or participating in (for patients) the program; and 3) views on how ALDER could be added as an adjunctive component of deprescribing programs in the future. **[Aim 3 clinician recruitment, screener, and consent form, along with clinician/patient interview guides will be added as a modification prior to beginning this portion of the study.]**

9.0 Research with Vulnerable Populations

N/A

10.0 Incomplete Disclosure or Deception:

N/A

11.0 Consent Process:

Online consent for all aims will be taken through a REDCap electronic consent form. Participants will be given time to read through the consent form and call or email study staff with any questions before they choose to consent or deny. Participants will consent electronically by entering the date and by typing their full name into the form, which will represent their electronic signature. Participants will be considered "consented" only if they provide both items (date and electronic signature). Consent will be time-stamped and participants will be able to save, download, and/or print a copy of the consent form for their records. Participants may also email the project director to request a copy of the consent form at any time.

We have included the language for the Certificate of Confidentiality and HIPAA Authorization, which explains the information we will be accessing from the Electronic Health Record, only for the purposes of the study and only for a specific amount of time. A partial HIPAA waiver is requested for Aim 1 for recruitment purposes.

Participants can consent to be contacted for future studies.

The online consent forms for Aims 1 and 2 have been uploaded with this submission. Clinician consent form for Aim 3 will be uploaded for IRB review prior to initiating that phase of the project. Because the Aim 2 consent form will include Aim 3 procedures, a separate consent for Aim 3 is not required for patients enrolled in the trial. However, a separate consent for Aim 3 clinic staff is provided.

If a participant chooses to withdraw during the study, their data will be retained up until their point of withdrawal. When a participant withdraws, they will no longer receive future assessments and they will no longer receive daily reminders to log-in to the website.

12.0 Waiver of Participant Signature on Consent Form:

N/A

13.0 Waivers and Alterations of Consent Information:

N/A

14.0 Financial Compensation:

Aim 1 and Aim 3 interview and focus group participants will be compensated $100 via a gift card. They will be sent their compensation following their participation in an interview or focus group.

Aim 2 participants will receive a $50 gift card following the completion of their post-intervention assessment.

15.0 Audio/Video Recording/Photography

Interviews and focus groups will be conducted on Zoom and audio recorded. Once recorded, the audio files will be transferred to a secure and password-protected server (NU Sharepoint) and will only be accessible to IRB approved research staff. All other copies of the recording will be deleted. The audio files will then be transcribed and deleted.

The transcripts will be fully deidentified and kept on NU Sharepoint. They will be organized, managed, and processed for analysis in Dedoose.[61] Qualitative analysts (Drs. Addington, Moskowitz, TBN postdoc) will analyze transcripts using a rapid qualitative synthesis approach[62] that captures "what works" (Plus), "what needs to be changed" (Delta), and additional insights. Final categories will be determined based on group discussion, including with the stakeholder panel. Findings from Aim 1 will be used to adapt ALDER intervention content and implementation strategies, which will be documented, respectively, using the Framework for Reporting Adaptations and Modifications-Enhanced (FRAME) and FRAME-Implementation Strategies (FRAME-IS),[63,64] and reported according to criteria for rigor in qualitative research. Results from Aim 3 will be interpreted with guidance from the stakeholder panel and used to inform future directions.

16.0 Potential Benefits of this Research:

There is no guaranteed benefit from participating in ALDER; however, participants might enjoy the skills taught in ALDER and continue practicing them beyond the online course (e.g., keeping a gratitude journal, completing everyday chores mindfully, or listening to a breath awareness meditation recording). Participants may gain mindfulness skills, regularly capitalize on positive events, or use positive reappraisal to reassess daily stressors. Even after completing the course, participants are encouraged to keep using their favorite skills, whether formally through the website and/or journaling about their experiences, or informally in their everyday lives. We hypothesize that participants in the ALDER pilot trial will experience increased positive emotions and decreased distress, anxiety and sleep disturbance. Results from this study may clarify a successful approach to integrating an online positive emotion intervention into clinical care aimed at managing symptoms such as anxiety and supporting BZRA deprescribing.

17.0 Potential Risks to Participants:

Possible discomfort while interacting with the ALDER platform

ALDER is relatively easy to administer and is a low-cost intervention. A potential risk of discomfort might arise with participants who do not have extensive experience using the internet, a tablet/computer, or mobile device. Participants might experience frustration or delayed onboarding if they are less familiar with using computer applications, browsing the internet, or connecting to wireless internet. The ALDER BrightOutcome website will be optimized for mobile use to minimize frustration when accessing the website on a smartphone. Participants will be able to contact IRB-approved study staff for technical support, if needed.

Possible discomfort when responding to questions

The risks of participating in ALDER are minimal. In past research, we have not observed any participants experiencing serious or lasting distress in response to similar interventions or assessments. The intervention has been user-tested to remove any material/content that might be upsetting or insensitive, to reduce the chances of using those questions in future versions. Therefore, the risk of discomfort is extremely low. However, some might experience slight discomfort when asked about their emotions, anxiety, stress, and coping. Participants are notified that they may skip any questions they do not wish to answer. Declining to answer any questions, declining to participate in the study, or declining to continue with the study once enrolled, will not have any impact on a participant's medical care at Northwestern Hospital or any affiliated specialty or primary clinics.

Potential loss of confidentiality in data

The risk of loss of confidentiality is extremely low. Identifiable information will be collected using REDCap which uses industry-standard encryption to protect participants' information while in transit from the moment data is entered to the moment it is stored on HIPAA compliant servers. Data is never fed back to participants or displayed on the participant website. Access to REDCap is granted to key personnel and all study staff handling personally identifiable information will have taken the CITI Human Subjects Training Course. Participants will be assigned and identified by a unique Study ID on the ALDER platform, and their information will be stored in encrypted forms on Northwestern computers. Any hard-copy documents will be stored in locked cabinets in the Department of Medical Social Sciences and all electronic copies of data, study emails, or records will have double-protection through password-protected access for NU servers and REDCap. Even if a participant's account is later compromised, submitted information on the website is protected and not released.

The ALDER online platform is hosted by BrightOutcome and is protected by end-to-end encryption and password measures. Participants will be able to access ALDER intervention on their computer browser or on their mobile phones with an internet connection. Participants will submit their home practice (e.g., gratitude journal) through the website. IRB-approved NU study staff will be able to access the data collected through the platform through direct export. No data will be stored locally on mobile phones nor participants' computers. All data will be collected directly through the website and stored on password-protected, secure NU servers.

Potential loss of confidentiality in general

Once a participant is enrolled in the study, there is the chance someone might see a participant filling out assessments or reading the positive emotion skills on the platform. To protect participant privacy, we encourage participants to be aware of their location (i.e., in a public or crowded space) when completing the online ALDER course and filling out their online assessment. Since the assessments are completed online, this allows for flexibility and participants can answer the questions from the comfort and privacy of their own home on their mobile device/tablet computer/laptop etc.

"Pollyanna"

The risk of proclaiming the importance of positive affect in the stress and coping process is that it may appear to minimize the pain and serious individual and societal consequences associated with major stressful events. We are not advocating a simplistic "don't worry-be happy" approach nor do we believe that simply increasing positive emotion will prove to be a cure-all for the very real and complex issues facing older adults who are candidates for BZRA deprescribing. Such a Pollyanna-ish stance could easily degenerate into blaming the victim for not thinking the positive thoughts that may prevent depression or other negative consequence of enduring stress. However, we argue that an intervention to increase positive emotions in patients sets the stage for a cascade of adaptive consequences, including reduced burden and improved quality of care. Ultimately, given the high level of comorbidities and lack of mental health care for older adults using BZRAs, we consider increasing positive emotion to be an inherently worthwhile intervention goal.

While our study focuses on positive emotion, we emphasize that ALDER is not a replacement for therapy, nor is it considered a treatment for depression or anxiety. Participants are encouraged to follow the guidelines of their health care clinician and advised that they should not put off starting therapy and/or medication or stop treatments recommended by their health care clinician.

Withdrawal of participants

If a participant wishes to withdraw, they can communicate this on the phone or via email to the project director or other designated study staff. Study staff will also be monitoring communications and potential withdrawal requests coming through on the study website and study email. The participant will then be promptly withdrawn from the study, their data collected and eventually analyzed only up until the point of withdrawal. No further data will be collected after a participant has been withdrawn. We will document the reason for withdrawing. We do not foresee any circumstances under which participants will be withdrawn from the research without their consent.

Possible risk of benzodiazepine withdrawal and worsening of symptoms

Though this study does not involve directly deprescribing BZRAs for patients, there are still standard of care risks for patients who wish to decrease their use of BZRAs, whether or not they choose to participate in ALDER. These risks are especially relevant for Aim 2 participants who may decide, in conjunction with their healthcare clinician, to decrease their use of BZRA medications. Risks include withdrawal symptoms such as gastrointestinal symptoms, tinnitus, sensory hypersensitivity, muscle twitches, perceptual disturbances, hallucinations, depersonalization, cognitive impairment. Research has demonstrated that the risks of symptoms worsening during deprescribing are small and are usually mild and short-term insomnia, anxiety, and restlessness.[65] Risks will be minimized by weekly monitoring and reporting of elevated withdrawal scores to the prescribing clinician. See the Data Monitoring Plan to Ensure the Safety of Participants below for a detailed description of monitoring procedures.

18.0 Provisions to Protect Participant Privacy and Data Confidentiality:

The research team is committed to the protection of human participants. All study staff will participate in initial training, follow-up training, and ongoing monitoring and supervision to ensure understanding of ethical issues involved in this research. This includes, but is not limited to, the CITI Human Subjects course, training on HIPAA, and measures to protect confidentiality. The research team will also be trained on how to use the REDCap Database, which is encrypted, password-protected, and maintained by the Northwestern University Clinical and Translational Sciences Institute (NUCATS).

The protocol to conduct the focus groups and phone interviews will be followed by study staff in order to protect identifiable information. For example, the study team will conduct the interviews and focus groups in a private room with a closed door, and participants will be advised to participate from a private setting. All audio recordings of focus groups and interviews will be transcribed with all identifying information removed, and the audio recordings will be deleted following transcription.

All data is stored and handled in a confidential manner and will only be stored on HIPAA compliant, password-protected servers accessible to IRB-approved study staff. Participants will not be identified by name on study documents or data shared with outside collaborators. Participants will be assigned and identified by their Study ID and all documents will be held to strict confidentiality and HIPAA compliant standards on encrypted and password protected servers. Confidentiality will be maintained through all phases, including data analysis and publication.

Identifiable information will be collected using REDCap which uses industry-standard encryption to protect participants' information while in transit from the moment data is entered to the moment it is stored on HIPAA compliant servers. Data is never fed back to participants or displayed on the participant website. Access to REDCap is granted to key personnel and all study staff handling personally identifiable information will have taken the CITI Human Subjects Training Course. Participants will be assigned and identified by a unique Study ID on the ALDER platform, and their information will be stored in encrypted forms on Northwestern computers. Any hard-copy documents will be stored in locked cabinets in the Department of Medical Social Sciences and all electronic copies of data, study emails, or records will have double-protection through password-protected access for NU servers and REDCap. Even if a participant's account is later compromised, submitted information on the website is protected and not released.

The ALDER online platform is hosted by BrightOutcome and is protected by end-to-end encryption and password measures. Participants will be able to access ALDER intervention and enter their skills practice (e.g., gratitude journal) on their computer browser or on their mobile phones with an internet connection. IRB-approved NU study staff will be able to access the data collected through the platform through direct export. No data will be stored locally on mobile phones nor participants' computers. All data will be collected directly through the website and stored on password-protected, secure NU servers.

Electronic files and study emails are protected on the departmental server at the Department of Medical Social Sciences. All data remains confidential, and any published results are de-identified. Data will be stored on the password-protected, encrypted server for 7 years after the completion of the study per IRB policy. Dr. Addington (Principal Investigator) is the Primary Custodian for the data. The backup to the primary custodian will be statistician Kathryn Jackson.

19.0 Data Monitoring Plan to Ensure the Safety of Participants:

We have developed the following data and safety monitoring plan. The pre-formative phase of ALDER will collect data on acceptability of various portions of the intervention.

The interviews, focus groups, assessments, and intervention sessions pose no more than minimal risk to participants. The data and safety-monitoring plan identifies the PI as the primary monitor of risks to human subjects in the form of data and safety related risks. Prompt reporting of serious adverse events will be reported to the institution's IRB and project officer of the funding source by the study PI. Risks, monitoring procedures, and reporting and action plans are described below for both data and safety related risks.

Data Risks and Monitoring

Data related risks. Data related risks to participants could consist of circumstances where an insufficient amount of data was collected to answer the research questions.

Data monitoring procedures. Overall recruitment goals, missing data, and follow-up failures will be monitored by the study director, who will provide regular updates and maintain constant communication with the PI and co-Investigators. Investigators will provide guidance on the study protocol, oversee the process, and adapt the protocol or suggest modifications as needed. The PI, Dr. Elizabeth Addington, will be the primary data custodian for ALDER.

Data risk reporting and action plan. The backup to the primary custodian, statistician Kathryn Jackson, will oversee the data safety and monitoring plan, data management, and data security. She will compile the recruitment numbers during all phases of the study and be responsible for assuring completion of required assessments, maintaining databases, and identifying missing data and missing follow-up assessments. Ms. Jackson will prepare recruitment and missing data reports for monthly review by the PI. Upon recognition of unacceptable recruitment, follow-up rates, or missing data, the investigators will intervene with strategies to remedy the shortcomings or provide additional monitoring.

Safety Risks and Monitoring

Safety related risks. Safety related risks could consist of:

1. Emotional discomfort while using the ALDER platform
2. Emotional discomfort while completing interviews, focus groups, or assessments
3. Loss of confidentiality in data
4. Loss of confidentiality in general
5. "Pollyanna" effect and mistaking the intervention as therapy
6. Signs of distress or revealing identifying information on the ALDER platform
7. Risk of benzodiazepine withdrawal and worsening symptoms

Safety monitoring procedures. All safety related risks will be monitored routinely throughout the study. Dr. Elizabeth Addington will be the main point of contact and the study advisor for questions regarding

safety concerns. She will help the team make recommendations and take research precautions to ensure the safety of our participants. (1-2) It will be made clear to participants that they are allowed to skip any exercises or questions that may cause them emotional distress. Participants are provided instructions on how to use the website, log-in, access the course, and are given the contact information of the Project Director, PI, and the designated study email. Participants can email or call study staff and the study is generally staffed Monday-Friday 9am-5pm except holidays, etc.

Study staff will monitor the website weekly and will be trained to respond immediately to participant needs and/or questions on technology and the platform. There is also a FAQ page on the website for frequently asked questions. If a question is not listed/answered on the FAQ page, participants may call or email study staff. Based on our experience conducting prior trials of online self-guided delivery of positive affect skills (e.g., LEAF, LARKSPUR, MARIGOLD), the study team is well versed in handling/managing instances that might require providing participants with additional resources.

(3) The security of confidential information will be monitored regularly. Participants will be informed that their responses will be kept confidential and not used against them in any legal, medical treatment, or any other manner. (4) Study staff will conduct interviews, focus groups, and other participant calls in a private setting with a closed door for participant confidentiality. Participants are encouraged to participate in a private space and to be mindful of where they complete their online assessments, so as to limit the chance of someone overseeing their answers on their computer/tablet/phone screen.

(5-6) In the event that a participant contacts the study directly to report severe distress or suicidality, or reveals this information online in an email or via the ALDER platform, the project director or a study team member will immediately alert the clinical psychologist (Dr. Elizabeth Addington) so that PD and Dr. Addington are immediately aware. Dr. Addington and the PD will work together to assess the situation and take immediate, appropriate steps. Designated research staff will promptly respond to a distressed participant with appropriate information about how to seek help. In previous studies, we have developed monitoring plans for responding to signs of distress in eHealth trials; an updated version of this protocol, tailored for the ALDER pilot trial, is included in the eIRB materials for this project. Based on our past experience conducting online studies with similar features (e.g., LEAF, LARKSPUR, MARIGOLD), the risk of these occurrences is minimal and the study team is well versed in handling/managing these instances, if they happen. In addition, within REDCap, we have set automatic flags to monitor responses to the following item within the PROMIS CAT for depression, “I felt I had no reason for living.” Because we are using the CAT administration of this measure, not all participants will be asked to respond to this item. For those who do receive this item as part of the PROMIS depression CAT, any response more than “Never” (i.e., rarely, sometimes, often, or always) will be flagged within REDCap and will automatically trigger an email notification to the study team, who will then follow the attached safety protocol (see “template telephone response for possible SI").

(7) For Aim 2 participants who may decide, in conjunction with their healthcare clinician, to decrease their use of benzodiazepine receptor agonist (BZRA) medications, risks include symptoms such as gastrointestinal symptoms, tinnitus, sensory hypersensitivity, muscle twitches, perceptual disturbances, hallucinations, depersonalization, cognitive impairment. Research has demonstrated that the risks of symptoms worsening during deprescribing are small and are usually mild and short-term insomnia, anxiety, and restlessness[65]. As ALDER does not involve directly deprescribing BZRAs to patients, these are standard of care risks for patients who wish to decrease their use of BZRAs, whether or not they choose

to participate in the study. Risks will be minimized by weekly monitoring and reporting of elevated withdrawal scores to the prescribing clinician. Standard guidelines for tapering of benzodiazepines recommend a slow taper, targeting a dose reduction of benzodiazepines no faster than a 25% reduction every 2 weeks and no more than 10% per week. As withdrawal symptoms may increase as patients approach the end of the taper (i.e., reach around 25% of their original dose), standard guidelines suggest decreasing the dosage at this point by no more than 10% every 2 weeks. While these are the standard guidelines for deprescribing BZRAs, patients will work with their prescribing clinician to decide on a schedule that best fits their healthcare goals. Therefore, each patient's individual tapering schedule may differ from the one outlined above. To monitor for risks of withdrawal, we will administer the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) weekly. If the patient has a BWSQ score of greater than 20 points, 2 or more severe symptoms, or endorses hallucinations, we will contact the patient and their prescriber to facilitate clinical follow-up with the patient's existing healthcare clinician.

Safety risk reporting and action plan. Any participant in need of treatment due to distress will be referred for appropriate services by study staff. In severe cases, the PI will be informed immediately. The study staff will report breach of confidentiality risks incurred by participants to the PI. The PI will be responsible for informing the IRBs and the Project Officer immediately of any life-threatening incidents (although this risk is very low and not expected to happen). The PI will take appropriate action to stop the study, release a participant from the study, or modify procedures to reduce and/or eliminate the occurrence of the abovementioned risks occurring at an unacceptable level.

Adverse events. All adverse events will be tracked and the PI informed within 24 hours to assess the situation and follow-up. An adverse event form will be developed detailing the problem, actions taken, supervisor notes, and follow-up steps performed. The form, supplemented by regular session notes will be immediately sent to appropriate agencies, including the IRB and US Deprescribing Research Network (USDeN). Any action recommended by one of the IRBs will be conveyed to the USDeN. The PI will be responsible for the monitoring and reporting of any adverse events. The co-investigators will be consulted as appropriate.

All problems having to do with subject safety will be reported by the Principal Investigator to the IRB within ten working days. Specifically, the following will be reported, in writing:
1) all serious adverse events associated with the study procedures, and/or 2) any incidents or problems involving the conduct of the study or participation, including problems with the recruitment and/or consent processes. The Principal Investigator will provide a discussion of any problems noticed during each year in the course of the study to the IRB and USDeN on an annual basis.

If, during the course of communicating with study staff (e.g., synchronously on phone/video or asynchronously via email), a participant indicates severe elevation of distress or possible suicidal ideation, study staff will follow the attached Safety Protocol, which has been developed by Dr. Addington (PI and licensed clinical psychologist), based on procedures used in their prior studies of positive emotion skills delivered online. Staff who are responsible for communicating directly with participants will be trained on the Safety Protocol by Dr. Addington. Trainees will be responsible for reading the entire Safety Protocol prior to training. Then training will include: a discussion/review of all elements of the Safety

Protocol; time for all trainees to discuss any relevant experience and ask questions; and the opportunity to role play using the telephone template responses.

20.0 Long-term Data and Specimen Storage and Sharing:

- Pre-screener and consent data will be collected and housed via REDCap at Northwestern University.
- Assessment data at 2 time points (T1 & T2) will be collected through REDCap hosted by Northwestern University and managed under the Northwestern University Clinical and Translational Sciences Institute (NUCATS). This secure server is password-protected, HIPAA-compliant, and protected by end-to-end encryption.
- Adherence data and daily home practice data will be collected through the online platform hosted by BrightOutcome and overseen by ALDER study staff at Northwestern University. The ALDER platform will be a tailored version of a course previously designed for dementia caregivers (LEAF 2.0). Participants will be able to take the online intervention through the platform accessible via the website on their computer browser, or the website on their mobile phones. Participants will submit their home practice (e.g., gratitude journal) through the website. Study staff will then be able to access and export the data collected through the platform. No data will be stored on mobile phones. All data will be collected directly through the website and stored on secure NU servers. The online platform is also HIPAA-compliant, password-protected, and secured by end-to-end encryption. BrightOutcome is not involved in using any of the data collected for research purposes via participants' interactions with the ALDER online program hosted by BrightOutcome.
- All participants will be able to access the website on their mobile phone and web browsers, but data will not be stored locally on mobile phones nor on web browsers. All data will be collected directly through the website and stored on secure NU servers.
- Dr. Addington, PI, is involved in the development of the online intervention, analysis, data interpretation and manuscript write-up. She will have secure access to the data housed at NU. No other Northwestern personnel will have access to the data unless they are listed on the IRB as study personnel. Dr. Addington and her NU collaborators will also use statistical programming on FSM desktops/computers and store analysis documents on FSM servers.
- Data, video recordings, manuscript drafts, forms and other study-related documents will be stored on secure FSM servers through the Department of Medical Social Sciences (MSS). For the information that must be identifiable for the purposes of the study (i.e., name, phone number, email address for participant contact), this information will have added layers of protection (via password access to the file). Participants will be coded and identified by a unique participant ID.
- Data input, processing, tracking and storage will happen at Northwestern University. Dr. Addington has oversight over each part of the process.
- Path to storage: BrightOutcome platform, REDCap platform, and audio/video recordings (input/collection) --> Northwestern HIPAA-compliant server (storage and analysis) on the FSMFILES MSS Departmental Server.

Identifiable data will only be shared internally amongst NU researchers listed on the IRB. Only IRB-approved individuals will have access to data through encrypted networks like the FSMFILES network or have permission to download datasets directly from REDCap (i.e., the PI, the biostatistician, the project director, IRB-approved study staff). De-identified data might be shared with collaborators for the purposes of data analysis, secondary data analysis, manuscript-writing, using Northwestern Sharepoint and Teams. We will take precautionary measures to protect the confidentiality of our participants.

21.0 Qualifications of Research Team to Conduct the Research:

The proposed project will be based in FSM's **Department of Medical Social Sciences (MSS)**. MSS was established in 2009 and provides a unique scientific home for applied researchers, integrating biomedical and social science approaches to improvement of health and health care delivery in diverse populations across the lifespan. Research themes include health measurement, quality of life measures, developmental mechanisms of health and disease and statistical tools to support clinical research with strength in application to specific disease processes such as cancer, neurologic disease, and early onset psychopathology. MSS is a catalyst for scientific integration across biomedical and social / life sciences campuses. MSS research cuts across traditional disciplinary boundaries, with collaborative ties with a broad range of research institutes and clinical departments across the University.

MSS has its own internal Information Technology group that manages all hardware, software, and support needs for the department. Department computers are generally on a three-year replacement cycle and use whatever technology is current at the time of replacement. The computers use either Windows or MacOS operating systems and run individual firewalls, antivirus, backups, and disk encryption that are centrally managed. Servers, while managed by the department IT group, are hosted at the University Data Centers that are shared by all departments. Servers provide web services, database services, file storage, and print services. These are secured behind Data Center firewalls with specific ports open for each specific service. Network access is limited to authorized University IDs. Physical access is limited to specific IT personnel using three factor authentication including biometrics. Files are backed up daily and databases are backed up every two hours. The department currently utilizes 24 servers in a combination of physical machine and virtual machine configurations. Protected health information and personally identifiable information that are stored on MSS database servers and on MSS file servers are layered with various physical and electronic access protections and policies to ensure HIPAA compliance.

In addition, we will be working with **BrightOutcome,** a healthcare technology company led by DerShung Yang, PhD (President), who has built successful collaborations with other investigators at MSS. Drs. Addington and Moskowitz have successfully partnered with BrightOutcome to build and host websites for numerous positive emotion intervention projects. Dr. Yang has been head of BrightOutcome since 2003 and has worked with other clients such as the Centers for Disease Control and Prevention, the National Institute of Mental Health, the National Institute of Nursing Research, and the National Cancer Institute.

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