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Study Protocol and Statistical Analysis Plan
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Title of Protocol: First CRUSH: Piloting the preliminary feasibility and acceptability of the Competence in Romance and Understanding Sexual Health (CRUSH) Curriculum

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Specific Aims /Objectives

There are currently no evidence-based interventions to improve the dating and sexual health of autistic adults. We have developed a curriculum, CRUSH: Competence in Romance and Understanding Sexual Health, to address this critical gap. We propose to conduct a 12-month pilot program of ~20 CRUSH curriculum sessions for 8-10 participants to acquire initial feasibility and acceptability data. We will use these data to make any needed changes to the curriculum to enhance future feasibility and acceptability. We will also test the feasibility and acceptability of the measurement battery for potential inclusion in future clinical trials. This preliminary information will also be used for subsequent extramural funding applications to test target engagement and efficacy of the intervention.

Aim 1: Acquire feasibility and acceptability data for delivery of the CRUSH curriculum in a group didactic setting plus 1-1 coaching. We will provide the CRUSH curriculum to 8-10 participants and then, following each intervention session, conduct a focus group to elicit feedback about the format, content, and delivery of each session. We will also collect formal acceptability ratings from participants and therapists after each intervention session and a longer survey at the midpoint and the conclusion of the intervention. We will explore feasibility by evaluating whether therapists can complete the planned content for each session and by examining participant attrition. We hypothesize that the CRUSH curriculum will be feasible and acceptable, and we will incorporate novel insights emerging from participants in future iterations of the intervention.

Aim 2: Acquire feasibility and acceptability data regarding the assessment battery for future clinical trials. Participants will complete a brief battery of target and outcome measures at baseline and post-intervention completion. We will collect acceptability data about the battery using a brief questionnaire after each assessment visit. We will evaluate feasibility by debriefing with participants after each measure by selecting a subset of items and asking participants to explain their understanding of the questions and response options. We will also examine patterns of missing data. Study staff will review questionnaires for completeness while the participant is present, and ask participants to complete missing items or provide a qualitative explanation for their inability to complete items. We will work to implement any changes suggested by participants to improve their overall experience at various data collection points. We hypothesize that the assessment battery will be feasible and acceptable to deliver.

Design and Methods

a. Study Design We will pilot ~15-20 CRUSH curriculum sessions with 8-10 participants. We plan to have two clinicians administer the curriculum. The measurement battery will be administered at baseline and immediately post-intervention. Feasibility and acceptability assessments will occur at each assessment session as well as the midway point and end of the intervention period.

b. Patient Selection and Inclusion/Exclusion Criteria We will enroll 8-10 (at least 2 women) 18-30-year-olds with documentation of an existing diagnosis of autism spectrum disorder (or access to services because of ASD). Other psychiatric comorbidities (e.g., anxiety, ADHD) will not preclude participation. We will include only participants who are able to demonstrate communication skills required to understand study procedures, risks and benefits, and intervention and assessments that are presented in English.

Participants will be recruited from our prior study – Development of a mechanistically-targeted skills manual for improving dating skills and increasing sexual health among adults with autism (CRUSH) IRB-P00019641 – if they met eligibility criteria, live within 35 miles of BCH, and expressed an interest

in participating in future studies. Should we need to recruit additional participants, we will recruit participants from BCH's Autism Spectrum Center (ASC), the Division of Developmental Medicine (DDM), and the Research Participant Registry (RPR; protocol 06-06-0261) in the Laboratories of Cognitive Neuroscience (LCN), and community sources such as local support groups, ASD associations, clinicians, ASD-themed events, special education groups, and websites via fliers and electronic recruitment materials.

Given ethical considerations surrounding the ability to provide consent, we will only include participants who are able to demonstrate communication skills required to understand study procedures, risks and benefits, and assessments that are presented or standardized in English. We will use the detailed protocol developed for IRB-P00019641 to screen participants and obtain consent (or assent in the case of adults with legal guardianship). It is described in the Human Subjects section and approved by the IRB at Boston Children's Hospital (BCH). Exclusion criteria will focus on factors preventing interpretation or valid engagement with the planned battery. Note: for participants who have already completed this screening protocol as part of IRB-P00019641, only current eligibility questions and study details will be discussed.

Inclusionary criteria for participants with ASD will include:

- (1) 18 to 30 years old;
- (2) Documentation of a prior diagnosis of autism spectrum disorder (ASD) or receipt of services based on an ASD diagnosis;
- (3) Ability to provide consent for the protocol and understand task demands. For any participants who are not recruited from IRB-P00019641 we will complete the WASI-2. In prior work, we have determined that adults with full scale IQ of 70 or above on the Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-2) typically meet this criterion, but a licensed clinician will review individuals who fall below an IQ of 70 on an individual basis to determine eligibility;
- (4) Fluent in English.

Exclusionary criteria for participants with ASD will include conditions that limit the ability to obtain valid data including:

- (1) Non-English-speaking participants (less than 50% of speech in English);
- (2) Known genetic etiology of ASD (e.g., Fragile X);
- (3) Major mental illness (e.g., bipolar disorder, schizophrenia, or psychosis).
- (4) Live more than 35 miles from Two Brookline Place where intervention sessions will be offered.

c. Description of Study Treatments or Exposures/Predictors The Competence in Romance and Understanding Sexual Health (CRUSH) curriculum is a draft of a sexual health manual for verbal autistic adults, ages 18-30, to be delivered in a group setting—with opportunities for 1-on-1 coaching and take-home assignments and activities to build requisite skills. The curriculum will be administered over ~20 group sessions. Coaching will be delivered by one of the study team members in a 1-1 session by phone, zoom or in person format, depending on the participant's preferences. All participants in the group will receive at least one 1-1 coaching session for each unit of the curriculum (at least 3 total) following a schedule. Coaching could be used to discuss take-home assignments, personal experiences or goals that require more attention than can be provided in a group format, or barriers to participating in the intervention. All participants will complete weekly take-home activities, which may include role play of new skills with trusted adults/friends/peers, generating behavioral scripts for new social situations, reflection on activities completed during sessions, re-watching video content from sessions, re-reading handouts, or observing real world social interactions and answering questions. Based on data collected from Dr. Faja's prior work (R03 MH113413), we have designed the curriculum to be iterative with repeating themes running throughout the curriculum (e.g., consent, effective communication skills). The sessions are organized into three over-arching units: (1) **Me:** getting myself "ready" for a relationship; (2) **You:** learning about your partner's perspective; and, (3) **Us:** how we engage in a

relationship together. Each session will consist of a recap from the previous week, review of the take-home activity from the previous week, introduction to the new content, learning opportunities for gaining the new skills (e.g., practice, demonstration, role play, video modeling), and takeaways and wrap-up of the session.

Our review of the extant literature and conversations with stakeholders revealed a gap in existing sex education curricula—behavioral skill development. This, to address this gap, we will also provide 1-1 coaching in which each autistic adult will collaboratively determine with a coach their own specific goals to work towards. The coach will also provide support for the take-home assignments, which will focus on individualized tailoring of the general topics and skills from the groups sessions. Using a coach provides a developmentally appropriate mentor to the adult rather than relying on parental input to explore one's sexual health. In sessions, we will use the evidence-based strategy of video modeling, which allows adults to re-watch if needed.

Some common themes that cut across sessions are: consent, self-efficacy, the concept that skill building requires practice including calculated and safe failures, awareness that there are multiple perspectives in relationships, communication skills for intimate relationships, recognition that each person has different needs, and social aspects of dating and sex.

d. Definition of Primary and Secondary Outcomes/Endpoints

Aim 1 - To assess the **acceptability** of the CRUSH curriculum, we will conduct a brief feedback interview to elicit feedback about each session. We will also use a 5-question qualitative interview to elicit individual feedback about each of the sessions beginning with a general question about the participant's overall experience, followed by specific questions about their favorite elements and least favorite elements, and whether there were any aspects of the session that were confusing, frustrating, or that made the participant uncomfortable. We will end with a question about how the session could be improved for the future. Interviews will be conducted within 48 hours of each session either in person or by phone. The co-therapists will debrief after each session about aspects of the session that went well or could be improved. After session 8 and at the conclusion of training, participants will also be asked about their overall experience of the CRUSH curriculum, whether they have noticed any positive effects in various key areas, and whether they have overall suggestions for improvement.

We will explore **feasibility** by evaluating whether therapists are able to complete the content planned for each session and by examining participant attrition patterns.

Aim 2 - We will pilot the primary measure of target engagement, the **Sexual Vocabulary Test** (Ousley & Mesibov, 1991), which we have updated and scored for pragmatic language (Kohn, Vidal, Chiao, Pantalone, & Faja, 2022) and the primary clinical outcome, The **Mathtech Behavioral Scale** (Kirby, 2013). Both measures will be collected at baseline and within two weeks of completing the CRUSH intervention. We will evaluate **feasibility** of these measures by debriefing with participants after each measure by selecting a subset of items and asking participants to explain their understanding of the questions and response options (i.e., cognitive interviewing). Staff will also note participant responses about items skipped/not understood/etc. The study team, including investigators, will review these records to discuss best strategies for changing the protocol (any changes to data collection will be submitted as an amendment). For example, if an item is consistently skipped or an instrument is consistently incomplete across multiple participants, that would be informative about the feasibility of that portion of missing data. Likewise, if participants do not engage with a portion of the intervention or drop out, we would examine their feedback about acceptability leading and demographics to guide potential revisions or modifications of future versions of the interventions. Following similar procedures to the PROMIS qualitative item review process (DeWalt, Rothrock, Yount, & Stone, 2007; Irwin, Varni, Yeatts, & DeWalt, 2009), cognitive interviewing with autistic adults will also confirm the

comprehension of each tasks or set of survey questions (Wolcott & Lobczowski, 2021). We will also examine missing data patterns within each measure to determine whether there are items that are too difficult, confusing, or burdensome for participants.

Acceptability will be evaluated via a 5-pt Likert scale to obtain participant ratings for each measure.

Name	Respondent	Type	Time	Items	Dependent Variables (DV)
Acceptability Interview	Autistic Adult	Interview	10m	5-10	Qualitative Data re. training session
Therapist Debriefing	Therapist	Survey	10m	6	Qualitative Data re. training session
Sexual Vocabulary Test	Autistic Adult	Survey	30m	20	Total Score (accuracy, pragmatics)
Mathtech Behavioral Scale	Autistic Adult	Survey	30m	54	Total Score, subscales
Cognitive Interview Script	Autistic Adult	Interview	25m	12	Qualitative Data re. assessments
Acceptability rating	Autistic Adult	Rating Scale	5m	2	<i>Ratings for each measure</i>
Background History Form	Autistic Adult	Survey	15m	36	Demographic information
FinalRatings–FirstCRUSH	Autistic Adult	Rating Scale	5m	10	<i>Ratings curriculum</i>

e. Data Collection Methods, Assessments, Interventions and Schedule

Recruitment will consist of distributing Institutional Review Board (IRB) approved materials (e.g., fliers, opt out letters, etc.) to identified referral sources. When individuals who are interested in participating or learning more about the study respond to/contact staff, an IRB-approved script will be used with each participant. During the initial phone call, research staff will provide standardized information about the study, determine interest, and ask standardized screening questions to determine eligibility. A protocol for screening competence to provide consent that is already approved by the BCH IRB and is in use in the Faja lab for adults on the spectrum will be used if the participant has not already completed another study in the Faja lab. This protocol also includes a detailed assessment of guardianship. If a participant with a guardian is eligible to participate, all required documentation will be obtained and reviewed following BCH guidelines (i.e., there are three levels of guardianship in Massachusetts, which require different levels of documentation and review by BCH; the BCH Division of Developmental Medicine staff are familiar with this process). Once participants are determined to be eligible for further participation in the study, staff will schedule the baseline visit and send the IRB-approved consent materials. Consent materials will include IRB-approved visual consent materials currently in use with adults on the spectrum for other protocols approved by the BCH IRB. Consent will be reviewed by study staff with the participant and, as appropriate, legal guardian and signed by the participant/guardian and staff member. Written assent will also be obtained from adults with guardians prior to beginning research activities.

Initial screening will be conducted by phone with potential participants (Call 1) to assess preliminary screening criteria and competence to participate. Screening may involve structured and open-ended questions to assess communication skills and comprehension (if not previously assessed). Documentation of a prior diagnosis will be obtained (or confirmed if previously obtained as part of the participant's participation in a prior Faja Lab study). Then, consent will be obtained from adult participant or their legal guardian.

Baseline performance on the Sexual Vocabulary Test and the Mathtech Behavioral Scale will be collected from all participants prior to the first CRUSH session. This session will either be in person or by zoom while the participant responds to surveys (on paper or via REDCap). Staff will be available throughout the session to assist with any items that are confusing or stressful and to ensure that the participant is responding and has adequate privacy while responding (either in a private room in the lab, or in a private space at their residence or another location of the participant's choosing). A subset of items will also be evaluated using PROMIS techniques including cognitive interviewing (as described

above).

The Background History Form collects basic demographic information about the participant and his/her household including access to transportation, internet use, and background related to sex education received in school. This information is essential for interpreting and reporting results as it provides information about variables that may influence the interpretation of other measures. The remainders of surveys are standardized measures that are used to gather information about the adult participant with ASD's knowledge and functioning in the dating and sexual health domains. All questionnaires/interviews will be adapted to ensure that they are understandable at an 8th grade reading level. Sexual terms will be paired with concrete examples.

Randomization and blinding will not be used for this feasibility and acceptability study. All eligible participants will be invited to participate in the CRUSH curriculum and the intervention team will assist with data collection about feasibility / acceptability as needed to facilitate rapid collection of information at the end of sessions and reduce participant burden. Before proceeding with acceptability questions, staff who deliver CRUSH curriculum the will ask whether the participant is comfortable providing feedback to them or would prefer to speak with another member of the research team.

CRUSH sessions will be scheduled once a week for approximately 15-20 weeks. Within 48 hours of each session, staff will collect the qualitative interview (in person at the end of the session or by phone)

At the midpoint of the CRUSH curriculum and again at the conclusion of the CRUSH curriculum, the two primary measures, the Sexual Vocabulary Test and the Mathtech Behavioral Scale will be collected again from all participants along with the Acceptability Interview for the Midway and Post-testing Sessions (Qualitative Interview for Session8 and FinalSession). These sessions will either be in person or by zoom while the participant responds to surveys (on paper or via REDCap) and interview questions. Staff will be available throughout the session to assist with any items that are confusing or stressful and to ensure that the participant is responding and has adequate privacy while responding (either in a private room in the lab, or in a private space at their residence or another location of the participant's choosing). At the final session, we will also collect 10 ratings about the participants' experience with the CRUSH curriculum overall. If participants are unable to provide that information at the final session, it will be collected at the post-testing session.

Adverse Event Criteria and Reporting Procedures

Adverse events will be assessed weekly throughout the intervention period (at the beginning of each CRUSH intervention session) using a 4 question checklist. Responses will be reviewed during the session break so that any potential adverse events can be discussed with the participant before they leave the session.

The Principal Investigator (Dr. Faja) will handle adverse events in consultation with experienced staff at the BCH IRB.

Quality Control Method

Dr. Faja will be responsible for quality and integrity of the data. The staff collecting data will be extensively trained in the use of all recording techniques with human participants. Quality control will be ensured by regularly meeting with study staff at all study sites and reviewing data collection and storage procedures, maintaining equipment, and processing data as it is collected to allow the early identification of potential problems with data quality.

Data Processing Plan

Behavioral Responses will be video recorded. Surveys will be programmed using REDCap. All lab-based behavioral responses will be scored using standardized coding manuals developed during the

piloting phase of the study. Responses will be scored by two independent raters who have achieved reliability $\geq .80$ on at least three scored protocols. Discrepancies will be resolved via consensus.

Data Analysis Plan

Interviews and focus groups will be recorded and transcribed. Two independent coders will analyze the qualitative data using conventional content analysis (Hsieh & Shannon, 2005) to detect themes relevant to intervention and task design. This analysis will be led by Dr. David Pantalone, an expert in qualitative data analysis and the lead on two qualitative manuscripts in preparation or under review from R03 MH113413 data with similar participants and content. Discrepancies will be resolved via consensus coding.

Median Likert ratings will be examined to determine whether tasks are neutral to positive. Acquisition rate will be calculated for each measure, using a cutoff of 60% (Little, Cohen, Dickersin, et al., 2012; Jakobsen, Gluud, Wetterslev, Winkel, 2017) in addition to examining the pattern of missing data.

Qualitative data will be used to update the CRUSH curriculum and measurement battery to improve feasibility and acceptability for a subsequent clinical trial. We predict that we will also demonstrate that the intervention and assessment battery are feasible and acceptable, given that the curriculum was designed with a high level of stakeholder input and an autistic adult co-authored the curriculum. As well, the measurement battery has already been used and refined based on data collection with autistic adults in the same age range as part of the R03 project conducted by our team. Should we find that our existing measures are feasible and acceptable, this will provide compelling preliminary data for a larger project. Data about acquisition rates will be critical for conducting power analyses and planning required sample sizes for a larger project. We will also obtain preliminary data about changes in target engagement and outcomes, which will demonstrate proof of principle for the CRUSH curriculum. In particular, we will examine whether there are individual improvements on these measures from pre-post intervention.

Statistical Power and Sample Considerations

The primary goal of this project is to obtain preliminary feasibility and acceptability data for a series of planned projects and provide sufficient information for development of a draft of a treatment manual. Because the planned analyses are qualitative and exploratory, power analyses are not presented. Instead, we selected the sample size based on the anticipated size of a single CRUSH treatment group. We plan to conduct a single group and will collect feedback from all group members.