Cover Letter

Official title: Developing a Down Syndrome Health Instrument
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PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR
Stephanie Santoro, MD

PROTOCOL TITLE
DEVELOPING A DOWN SYNDROME HEALTH INSTRUMENT

FUNDING
K23 - 1K23HD 100568-01A1

VERSION DATE
11/11/2021

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

Aim: The purpose of this study is to develop an instrument which measures health in individuals with Down syndrome (DS) as perceived by their caregivers.

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

DS is associated medical and psychological comorbidities due to extra genetic material from chromosome 21.[1] The health status of over 200,000 people with DS in the U.S. is unmeasured.[2,3] Outcomes such as life expectancy have improved over time.[2,4] Yet a direct measurement of health does not exist for DS. The WHO defines health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."[5] The incorporation of this framework cannot be easily applied to genetic syndromes, which, by definition, have associated medical and developmental comorbidities which differ from the general population.[6] DS also has a unique mental health profile, with increased rates of ADHD, autism, and Alzheimer's disease, among others.[7–9] Social factors, like community inclusion, school support and health care costs also impact those with DS to differing degrees than the general population.[10–12] **Due to differences in risk profiles for genetic syndromes, the condition-specific health of individuals with DS may not be accurately measured using health assessment tools developed for general population use.**

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

Research Design: The process of developing and validating a measurement instrument is iterative.
Figure 1 depicts the overall plan for creating a DS health instrument (DHI). The sequence of tasks is:

Phase I: Development of conceptual model with well specified constructs (or dimensions)
Phase II: Generation of an item pool of new and adaptation of existing items mapped to constructs
Phase III: Cognitive evaluation of items (face/content validity)
Phase IV: Reliability and validity analyses
Phase V (Future): Responsiveness, evaluation of sensitivity to change, test in Spanish-speakers

III. Proposed Experiments:

Specific Aim 1: To conduct focus groups among caregivers, individuals with DS, panels of experts on DS and primary care physicians, and cognitive interviews to refine a conceptual model of health for DS and create an item pool.

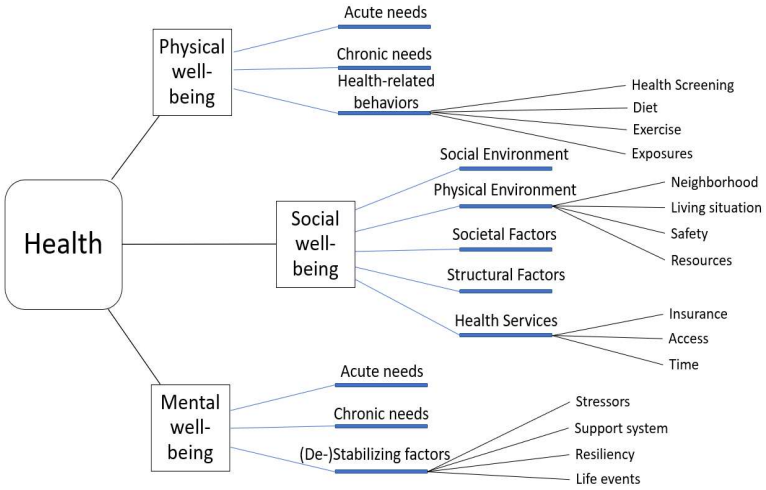

Figure 2: Conceptual Model of Health in DS based on WHO definition of health

Phase I: Consistent with the WHO definition of health, I created a conceptual model for health in DS (Figure 2). The hypothesized constructs (concepts) of the model and constituent concepts; physical well-being, mental well-being and social well-being, form the foundation for the DHI.[41–44] In Year 1 of this proposal, the model of DS health will be refined. I will share an electronic version of the outline with stakeholders (physicians, caregivers) and ask for feedback. This input will ensure that the conceptual model is comprehensive of DS comorbidities, includes impact on daily activities and is understandable.

Phase II: Due to the dearth of available scales to measure health in DS comprehensively, the available item pool is limited. Using items for the general population will require modifications to the item stem and response categories to capture the spectrum and range of health in DS. In Year 1 of this proposal, I will evaluate existing items to include in the draft item pool. If needed, permission to use items from these instruments will be requested. However, in my review of these existing instruments, none fully capture health; I anticipate that novel items will be needed. I will

draft a preliminary set of items on health aspects of DS for expert panel and focus group testing.

Expert Panels: Medical professionals providing care to individuals with DS (primary care physicians, subspecialists and DS clinic experts) and other relevant experts (social workers, teachers) will be invited to participate in an expert panel (N=16). In Year 1, I will lead the panel in discussion related to health, existing items and gaps in current measures of health. They will not only verify model constructs but review and add to items mapped to constructs. Two expert panels of 8 will occur in the MGH DSP conference room or will be conducted virtually through the PARTNERS-approved secure version of Zoom platform.

Focus Groups: Individuals with DS and caregivers of individuals with DS will be recruited from the MGH DSP and the local Massachusetts DS Congress (MDSC) to participate in focus groups as well as patients who have previously consented in Database protocol (Protocol #:2012P000828) to be contacted about additional research studies (N=42). In Year 1, I will lead these groups in discussion of health using a modified think-aloud approach with structured and unstructured probing. Focus groups will be audio-recorded and transcribed. Focus group discussion will be used to identify emerging themes / topics (e.g. prioritize, identify components of health) which will be used to refine the conceptual model, refine existing items, and generate items for DHI. They will be used to develop items mapped to constructs, thereby increasing item pool. Then the item pool will be evaluated using cognitive interviews. Approximately twelve focus groups of approximately 6 participants will occur in the MGH DSP conference room or will be conducted virtually through the PARTNERS-approved secure version of Zoom platform. Focus groups will be grouped by age to attain homogeneity of the group; group composition can impact participants' comfort to say what they think or feel.[45] The six groups will be enrolled with attention to factors such as age of child with DS, developmental level of child with DS, or other emerging factors. The rationale for the number of focus groups is to be able to have a focus group for each of the relevant age ranges cause you want homogeneity within groups, i.e., parents or caregivers whose kids may be dealing with same developmental issues.

Phase III: The cognitive evaluation of items will assess study item structure, format, and order. In Year 2, I will conduct face-to-face or virtual, Zoom-encrypted 60-minute cognitive interviews (CI) with caregivers (4 rounds with iterative refinement, total N=40) to refine the language and items. Participants will be recruited from the MGH DSP and MDSC. The cognitive interviews will provide information on terms used, evaluation of question stems and responses, feedback on how responses map to the response options, and show if the participants understand the survey items. CI findings will be used iteratively to inform the survey, and will be conducted in rounds (four groups of CI of 10 participants per round) to allow findings from the first round to inform the version of the survey tested in the second round. The CI will use a combination of think-aloud with proactive and reactive verbal probes, and will be audiotaped. At completion of Phase I-III, we hope to be able to end up with a final item pool of 70 that will be used for data collection and psychometrics.

Specific Aim 2: To administer the DHI and establish internal validity, reliability, and external validity of the DHI for use in clinical research.

Phase IV: I will create a DS health instrument which is able to be used to draw a valid inference about health and can establish some basic inferential validity (we are not

establishing causal validity). We will use a "unified" approach to validity, which emphasizes both psychometric evaluation as well as consideration and evaluation of the usefulness, relevance and intended use of the DHI.[46,47] This phase of the proposal, Year 2 through 5, encompasses data collection using survey methods as well as psychometric analysis.

I. Validation Approach: The purpose of conducting a validation and reliability evaluation of a measure is to determine the validity of the inferences that may be drawn from the measure within the population of interest. Any "validation" efforts may only support the assumption that the instrument is a valid measure for which to draw inference in a population that is comparable to the populations used to validate the measure.[46] Therefore, it is essential that the populations represented in the validation samples have some equivalence to the target populations in which the DHI is intended to be used.

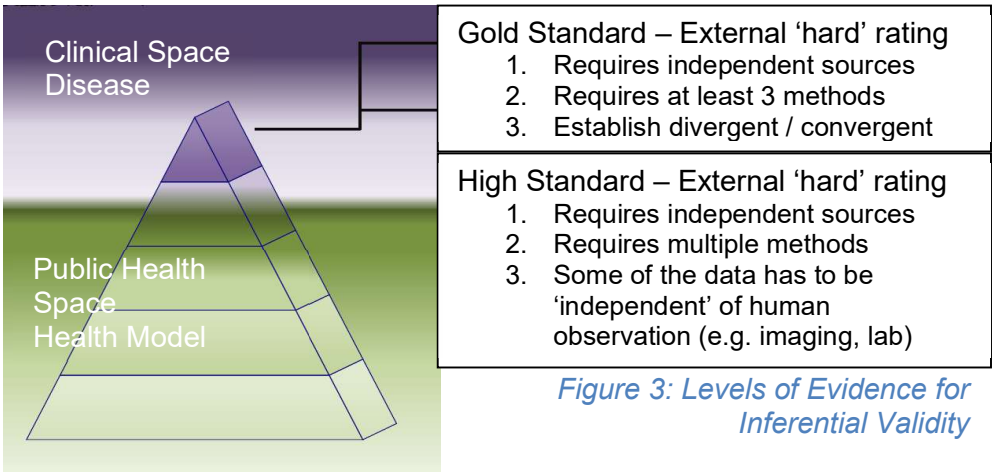

Figure 3: Levels of Evidence for Inferential Validity

A further consideration in validation approach is the intended use of the measure, this dictates the level of evidence required for inferential validity.[48–50] Figure 3 (M. Constantine, PhD and PLUS Consortium, email communication, Nov 19, 2018) shows the associated methods of hierarchical "levels" of evidence.[51] Criterion validity is based on the correlation of the measure to an external measure. More rigorous methodological approaches to validation are needed when higher evidence is needed. With the level of evidence achievable through this proposal, we will create an instrument validated for research in the clinical space at the "High Standard" level.

The intended use of the DHI is to draw inferences related to DS health across the US general population as reported by caregivers for clinical research. Proxy report will be used due to the range of intellectual disability in DS and to maintain consistency of respondent in all ages from pediatric to adolescents to young adults. Proxy report is often used in questionnaire research in DS.[52,53] Proxy respondent data has been found to be reliable.[54] Self-report measures in people with developmental disabilities are possible with appropriate design and modification.[55] Patient age will be restricted to <22 years to: 1) minimize the confounding impact of transition to community placement as adults with DS graduate high school, and 2) because there are not established health guidelines for adults as there are for children in the AAP guideline which is an anticipated source of external criterion measure to establish external validity.

We will additionally recruit a cohort of caregivers of individuals with autism spectrum disorder (ASD) to establish discriminant validity. By recruiting this cohort, we aim to show that caregivers who have children with DS and caregivers who have children with ASD answer questions differently. This will strengthen our DHI by showing that the survey is truly specific to DS and capturing DS-specific health.

Power calculation: Sample sizes are based on several criteria. The basic rule of thumb for psychometric analysis (primarily correlation analyses) is 10 subjects per survey item.[56] The current conceptual model includes 95 items, with refining in SA1, I plan a final item pool of 70 items. The current target sample sizes will support up to 70 variables (items) available for inclusion in psychometric analyses. For instance, if the final instrument contains 70 items, 700 subjects are sufficient for 80% power to detect a difference of ≥ .25 standard deviations using type I error of 0.10.

II. Population A. Sampling frames:

1. Local – MGH DSP: In Year 2, I will begin to administer the DHI to caregivers of patients <22 years of age with DS at the MGH DSP (Table 1). With an annual clinic volume of 500+ patients and a population invested in clinical research, we anticipate a response rate of >50% based on current research participation which equates to at least 200 local participants. With an estimate of 5 surveys per week, this will occur over 40 weeks.

Table 1: Participant Criteria

Inclusion criteria
Primary caregiver of an individual with DS (individual with DS age: <22 years)
Caregiver age: ≥18 years
Fluent in written and spoken English
Able to read and provide informed consent
Exclusion criteria
Physical or mental condition of caregiver that would prohibit self-administration of questionnaire
Mosaic Down syndrome (mDS): based on medical record review. If caregiver uncertain or unknown mosaicism, we will request additional records.

2. National – DS-Connect: The DHI is intended for use in the US DS population and it is critical that the validation include a national sample. The best sampling frame for the US population with DS is DS-Connect®, the national NIH contact registry for DS, as this best characterizes the population.[57–59] With a current registry of 4000+ members and a population who has registered with the intent to participate in clinical research, and whose involvement led to successful recruitment, we estimate a national sample of at least 500 participants in Year 3 and 4.[60] Specifically, there are 4000 patients of age 0-22. DS-Connect includes an initial health questionnaire which asks DS type (free trisomy, translocation, or mosaic) and can be used to focus only on those participants who do not have mDS. DS-Connect has their own process (with an application, committee review, etc), but we would request that our hyperlink by shared by email to their listserv / distribution list. Study team would not have access to individual emails. DS-Connect website require a username and password to be entered by study staff; Dr. Santoro is enrolled with a research account.

3. Validation with ASD cohort (Population B). We plan to recruit 100 primary caregivers of individuals with ASD. We plan to recruit locally through MGH clinics at the Lurie Center for Autism, as well as recruiting nationally by sharing our recruitment materials with autism affiliate organizations around the US.

B. Recruitment / enrollment: I estimate response rates of >50% locally and of 50% nationally based on interest in research participation in these populations (See **Recruitment and Retention** for examples of successful recruitment). Forty researchers over the past 4.5 years with online studies have done well with DS-Connect. After initial contact, I plan to contact non-responders two additional times. If response rates are

high, sample size may exceed expectations. Strategies for recruitment and retention may be used.[61]

1. Local - Caregivers will be recruited and consented in the MGH DSP; they will complete the DHI in-person in clinic or at-home with return envelope provided.
2. National - The national sample will be contacted electronically (email or posting on DS-Connect website and other social media platforms such as Facebook), as such, we plan to include fields in the electronic contact for interested participants to enter contact information or to complete an electronic version of the survey directly. This will consist of a link in the REDCap survey (at the very beginning) should participants prefer to share this information. Caregivers will be asked to: follow the electronic link to study information, complete the electronic survey or provide contact information.

Randomization: N/A

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

Study procedures:

a) Recruitment: Recruitment will occur in the MGH DS in-person in clinic, by sharing an electronic version of the study information sheet by email, and by posting a study information sheet online. The study information sheets will be for 1) the in-person focus groups/expert panels and 2) the survey.
    i. Recruiting focus groups / expert panels members: Interested participants will contact our study staff, to answer additional questions and coordinate scheduling for one of the focus groups or expert panels.
        i. From those interested in participating in the focus group, we will identify a subset of pairs of caregivers and adults with Down syndrome who both have an interest in participating. We anticipate that this will be 6 pairs (6 adults with Down syndrome and their caregiver). We anticipate that the caregiver will typically be a parent but could be a sibling or legal guardian.
            1. Adults with Down syndrome: When discussing the study with an adult with Down syndrome and/or his/her caregiver, the study staff will review implications of participating in focus group, and initially ask the caregiver if the adult with Down syndrome is able to provide verbal consent to participate in the focus group.

ii. Physicians and health care professionals: Interested participants will contact study staff via direct communication on email. Physicians and health care professionals will be required to give verbal consent to participate it the focus group.

ii. Survey: An information sheet will be shared with visitors of the MGH DS clinic and shared electronically to the national sample. The national sample will be contacted electronically (email or posting on DS-Connect website and other social media platforms such as Facebook), as such, I plan to include fields in the electronic contact for interested participants to enter contact information if they elect to receive a paper-and-pencil survey via mail or a link to complete an electronic version of the survey created in REDCap.[59] As outlined above, age, race and ethnicity will be considered at time of enrollment with stratification numbers outlined above. I anticipate that participants will be contacted up to three times during recruitment. Interested participants will be mailed a paper-and-pencil survey up to three times. After reviewing the study information sheet, interested participants will complete either verbal or electronic consent form. Details of recruitment stratified by age, race and ethnicity are listed (Table 1).

b) Consent: For all aims, informed consent will be obtained by the PI or her designated research coordinator. Method of consent will vary depending on the aspect of the study:

i. verbal consent for focus groups (caregivers and individuals with Down syndrome), expert panels (physicians and other health care professionals), and cognitive interviews(caregivers): In these components, participants will learn about aspects of the study including the potential risks and benefits. After addressing any questions or concerns, we will obtain participants' verbal consent indicating their understanding of the study procedures and their consent to participate.

i. Adults with Down syndrome: The PI, Dr. Stephanie Santoro, is a physician with experience providing medical care to adults with Down syndrome and has experience participating in research studies in which consent of adults with Down syndrome is obtained.

When the adult with Down syndrome and his / her caregiver arrive for the focus group, the PI will review aspects of the focus group, requirements, and assess the ability of the adult with Down syndrome to provide verbal assent, as well as confirm his / her assent in conjunction with caregiver's verbal consent.

ii. Caregivers: We anticipate that the caregiver will typically be a parent, but could be a sibling or legal guardian. If the caregiver is not a parent, and a legal guardian, we will require documentation of such. After documentation has been reviewed caregivers will have the opportunity to give verbal consent allowing them to participate in the focus group.

iii. Physicians and other health care professionals: When participants arrive to the focus group they will receive a copy of the focus group information sheet to review. Research staff will be available for discussion about the study. Physicians and other health care professionals will have the opportunity to give verbal consent to participate in the expert panel.

ii. waiver of documentation of consent for surveys: In the survey component of this study, we request waiver of written consent as this consent form would be the only record linking the subject and the research and the principal risk would be potential harm resulting from a breach in confidentiality; and the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context. In the national sample, an electronic version of the consent will be included at the introduction to the survey, with required checkboxes and an electronic signature indicating understanding and consent to participate. Consent is implied through completion of the electronic and written surveys. Research staff will be available in-person or by phone or email for discussion about the study.

All individuals have the option to elect not to participate in study activities and not to complete the electronic survey.

c) Focus groups / Expert panels: Will be audiorecorded and transcribed. We plan to use a digital audio recorder for this purpose; which we plan to purchase with grant funding (i.e. it will only be used for this project). Participants will give verbal consent to be audio-taped at the time they consent to participate in the focus group / expert panel. Participants will be instructed not to state anything that could individually identify themselves prior to the start of the recording. Audiorecordings will be stored on PI's password- protected, Partners desktop (by connecting record device to computer). Audio files will be stored on PI's folder on Partner's shared drive. Audio recordings be deleted from recording device upon upload. Audio recordings will be transcribed manually. All identifiable information, including the code key which connects unique ID back to identifiable information, will be stored on PI's Partners desktop. We may recontact participants up to three times, by email, after the focus group / expert panel is completed to gather any missing information, send thank you notes, or answer questions.

d) Instruments:

i. In the iterative process of instrument development, we will identify most appropriate instruments to map to constructs. Potential instruments include those in Table 2. Specifically, we have created a sub-survey with instruments from the Pediatric Quality of Life Inventory (PEDSQL)[c] SF12v2[b]. This survey will be self-administered electronically, contacted by either email, advertisement, or DS-Connect website. This survey has been created in REDCap and is titled "Parent Views of Health".

Table 2: **Potential** External Criterion Measures

	In comparison to the DHI, this measure is the…			
	Same source, same method	Same source, different method	Different source, same method	Different source, different method
Physical Well-being	Children's Sleep Habits Questionnaire[a] Reported exposures	Activity log Diet recall	Teacher-completed Vineland Adaptive Behavior Scale – 2nd Edition (VABS-II)[a] Physician survey	Vital signs: Body mass index (BMI) and blood pressure Apnea-hypopnea index HemoglobinA1C Physician completion of AAP guidelines
Mental Well-Being	Pediatric Quality of Life Inventory (PedsQL)[c] SF12v2[b]	Stressor checklist	Clinical Social Work assessment	Psychology, psychiatry and social work notes
Social Well-Being	Index of Well-Being[c] Personal Wellbeing Index (PWI)[c]	Clinic intake sheet regarding living situation	Teacher-completed Social Responsiveness Scale (SRS-2)[b]	Insurance type Income

[a] already validated in DS; [b] already validated in intellectual disability; [c] validated in general population only

e) DHI: A REDCap link to the survey will be sent via recruitment email to anonymously collect data.
f) Multivariate statistical correlations will be performed by the primary investigator or faculty of Mass General Hospital's Biostatistics Department.

Surveys or Questionnaires: The Down Syndrome Health Instrument (DHI) which will be created in the first aim of this study will then be tested in aim 2. We anticipate that the draft DHI will contain up to 70 items. Method: A self-administered survey of caregivers described above (In "Population:"). Mode: Either a paper-and-pencil or electronic survey will be used for local sample. The national sample will be contacted electronically (email or posting on DS-Connect website), as such, we plan to include fields in the electronic contact for interested participants to enter contact information. In the electronic contact, participants will elect to receive either a paper-and-pencil survey via mail or to complete an electronic version of the survey. The electronic version of the DHI will be created in REDCap with identical questions, formatting, language and response options as the paper-and-pencil survey.[62] I have personal experience with creating, designing and sharing electronic surveys in REDCap, a secure, web-based application designed to support data capture for research studies.[29,62,63] I plan to allow participants to choose the delivery mode to allow the DHI to be validated in the mode(s) most user-friendly to the participant. When planning future use of DHI, both paper-and-pencil and electronic modes would be conducive to use in a research setting. A codebook will be created for response verification and double data entry used for paper survey data entry. This survey does not contain any PHI or identifiable information.

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

N/a

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

Potential risks, discomforts, inconveniences and precautions

1. Known and potential risks

Responses on survey will be compared with external measures through medical record review. All PHI will be stored on the principal investigator's password-protected computer at MGH. There is limited potential for unanticipated disclosure of medical information, but this will be minimized through the Data and Safety Monitoring Plan.

- Procedures for protecting against or minimizing risk: For all aims, data will be collected and protected according to the procedures described above. Personal identifiable information will be viewed only by the minimum number of study staff required to perform a given task.
- Confidentiality: All assessment information will be considered confidential. Data will be organized in code-labeled binders and stored in locked cabinets.

  No participant will be identified by name in any presentation of the results. Identification numbers will code data entered for computer analysis, and the study staff will keep all names and code numbers in a password - protected folder.
- Adverse Events: I will oversee all procedures in real-time safety monitoring. Although unanticipated, I will immediately report any serious adverse event during any study related activity to the MGH IRB, and NIH. If any action is taken by the MGH IRB, I will report to the NIH in the appropriate time frame. In addition, I will review with my primary mentorship team to determine if any future changes are deemed necessary to the study protocol to minimize future risk.

2. Known and potential inconveniences

Time spent participating in focus groups, cognitive interviews, or in completing the anonymous survey; travel to Boston. Participants will be reimbursed for time, parking, and will be informed of the associated time commitment prior to consenting.

3. Precautions, risk minimization:

As above regarding data safety and management.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

As above. There are no anticipated safety risks associated. Participants are voluntarily participating in activities (focus groups, cognitive interviews, and DHI survey) and have the right to withdraw at any time.

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

As above, the primary risk is unanticipated disclosure of medical information and responses to study procedures (focus groups, cognitive interviews, survey). Potential psychosocial risks include discomfort answering questions (during focus groups, interviews, or survey). There is also the inconvenience of time spent completing the survey.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

Potential benefits

There is no direct benefit to participants. However, the information learned from this research study will provide general knowledge that may benefit individuals with Down syndrome and their families in the future. Lessons learned from the survey will provide a baseline for future efforts to improve health for individuals with Down syndrome.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

The study population will include caregivers of individuals with Down syndrome; see exclusion and inclusion criteria above.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied

participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

This project focuses on instrument development in English-speaking individuals. Creating an instrument across multiple languages would not be feasible, and would create potential for differences in interpretation (e.g. in item responses or question stem) which could actually be a result of slight differences in translation rather than the question itself. Ideally, we plan to create non-English versions in the future, but will first focus on English-speakers to prove our concept and then adapt to other languages.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Non-English_Speaking_Subjects.1.10.pdf

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

Recruitment:

1. Sampling: In Specific Aim 1, caregivers will be recruited from the MGH Down syndrome program (DSP) and the Massachusetts Down Syndrome Congress (MDSC). In Specific Aim 2, caregivers will be recruited from the MGH DSP and the national contact database, DS-Connect. In Specific Aim 3, caregivers will be recruited from the national clinical trials network (DS-CTN) and the MGH Pediatric Primary Care clinic. In these three aims, caregivers will meet inclusion criteria, including: primary caregiver of an individual with DS (individual with DS age: birth to 22 years), caregiver age ≥18 years, fluent in written and spoken English, able to read and provide informed consent. Participants with a physical or mental condition of caregiver that would prohibit self-administration of questionnaire will be excluded. In addition, in only the focus group component of Specific Aim 1, adults with DS (age 18-22 years) will be included in discussion regarding health views.
2. Recruitment: A study information sheet will be created. Recruitment will occur in-person in clinic, by sharing an electronic version of the study information sheet by email and posting of a study information sheet online. The national sample will be contacted electronically (email or posting on DS-Connect website and other social media platforms such as Facebook), as such, I plan to include fields in the electronic contact for interested participants to enter contact information if they elect to receive a paper-and-pencil survey via mail or a link to complete an electronic version of the survey created in REDCap.[62] As outlined above, age, race and ethnicity will be considered at time of enrollment with stratification numbers outlined above. I anticipate that participants will be contacted up to three times during recruitment. Interested participants will be mailed a paper-and-pencil

survey up to three times. After reviewing the study information sheet, interested participants will complete the survey; consent is implied through completion of the electronic and written surveys.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

Participants will be reimbursed for time ($25 / hour) and parking ($19). Refreshments will be provided for focus groups and expert panels.

For guidance, refer to the following Partners policies:

Recruitment of Research Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Recruitment_Of_Research_Subjects.pdf

Guidelines for Advertisements for Recruiting Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Guidelines_For_Advertisements.1.11.pdf

Remuneration for Research Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Remuneration_for_Research_Subjects.pdf

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

A. Consent / Assent: Informed consent will be obtained by the PI or her designated research coordinator as outlined above in Study Procedures.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects:
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Informed_Consent_of_Research_Subjects.pdf

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

Data and Safety Monitoring Plan.

- Procedures for protecting against or minimizing risk: For all aims, data will be collected and protected according to the procedures described above. Personal identifiable information will be viewed only by the minimum number of study staff required to perform a given task. Data will be collected from REDCap and reviewed monthly. Thorough review will be conducted by the Primary Investigator for the duration of the study.
- Other routine data protection available through MGH information systems network will also protect data from unwanted accessing.
- Confidentiality: All assessment information will be considered confidential. Data will be organized in code-labeled binders and stored in locked cabinets. No participant will be identified by name in any presentation of the results. Identification numbers will code data entered for computer analysis, and the study staff will keep all names and code numbers in a password - protected folder.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

- Adverse Events: I will oversee all procedures in real-time safety monitoring. In the event that a participant faces an adverse event, the PI will promptly report all adverse events (within 7 calendar days) to the Partners Human Research Committee as per the Reporting Unanticipated Problems Guidelines. Each report will include a detailed description and its relation to the research being conducted Although unanticipated, I will immediately report any serious adverse event during any study related activity to the MGH IRB, and NIH. If any action is taken by the MGH IRB, I will report to the NIH in the appropriate time frame. In addition, I will review with my primary mentorship team to determine if any future changes are deemed necessary to the study protocol to minimize future risk.
- Participants are voluntarily completing this survey and have the right to withdraw at any time. The final question asks if the participants have additional comments. Should participants completing the survey express distress or adverse events related to the instrument, the PI will follow-up by email.

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MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

To ensure protocol adherence and maintain the validity of the survey results research staff will be responsible for monitoring results periodically. Research staff will review completed surveys and remove surveys that do not meet study requirements prior to data analysis.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/DSMP_in_Human_Subjects_Research.pdf

Reporting Unanticipated Problems (including Adverse Events)
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Reporting_Unanticipated_Problems_including_Adverse_Events.pdf

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

Every effort will be made to maintain an individual's privacy; however, several groups will have access to the records, including the principal investigator, Massachusetts General Hospital employees involved with the research study, the Institutional Review Board, and the Office for Research Compliance and Regulatory Affairs.

The information from the research study may be published; however, participants will not be identified in such publication. The publication will not contain information about participants that would reasonably enable someone to determine their identity as a research participant. Data may be presented at scientific meetings or published in scientific journals in aggregate, de-identified fashion.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

n/a

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

Data will not be stored at collaborating sites outside Partners.

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

No data will be collected from entities outside of Partners. Although external entities, such as DS-Connect, may be used to give participants access to the DHI in REDCap, the survey will be administered using the REDCap system and all data/survey responses will be remain within the Partners system. Only Partners/MGH standard workstations and laptops being used for this research.