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PR-REACH Subprotocol of Clinical Trials Core: *PR-REACH's guideline for best practices in the informed consent process for clinical trials in Puerto Rico*

INVESTIGATORS AND INSTITUTION OF AFFILIATION

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RESEARCH QUESTION

- What are the attitudes and perceptions regarding the informed consent process of current clinical trial participants in Puerto Rico?
- What barriers and facilitators to the informed consent process in Puerto Rico do clinical research stakeholders identify?
- What do clinical research stakeholders recommend as best practices for informed consent in Puerto Rico?

HYPOTHESIS & SPECIFIC AIM

We hypothesize that the results from the surveys, interviews, and focus groups will uncover distinct barriers and facilitators to the informed consent process in a Puerto Rican context, different from those present in the United States of America. The factors described through community engagement and feedback will guide the development of a culturally tailored guideline detailing the best practices for the informed consent process in a Puerto Rican population.

BACKGROUND/SIGNIFICANCE

Clinical trials are critical for breakthroughs in care, but a lack of participant diversity limits the generalizability of their findings. Samples that truly represent a population allow us to understand how distinct factors impact the health of individuals from diverse experiences. With this insight we can act on the evidenced disparities. However, minoritized communities are underrepresented in studies. Today, researchers from the United States of America struggle to enhance representation even after the creation of the Nuremberg Code in 1947, the National Research Act in 1974, the

Belmont Report in 1979, and the Common Rule in 1991 –all dedicated to protecting human subjects and establishing ethical standards for clinical research–. Also, the NIH Revitalization Act of 1993 established guidelines to increase the recruitment of women, racial, and ethnic minorities. Mistrust is a common factor highlighted by minoritized people when deciding to participate in studies. We can find the origins of this sentiment in history. The Tuskegee Syphilis Study (1932-1972) and the 1989 genetic study of the Havasupai Tribe are examples of violations to community trust.

In Puerto Rico, the word “experiment” and its derivatives possess a negative charge. As a colony of the US, Puerto Ricans have been exposed to mistreatment in the name of science. Events like the studies from Cornelius P. Rhoads in the 1930s and the contraceptive trials of the 1950s marked public perception of research for generations. Other unethical projects include the US military occupation of Vieques to test Agent Orange (1960s) and bombs, which lasted from 1941 to 2003. Puerto Rico was also among the territories impacted by the herbicide testing (1950s-1960s), Project Sunshine (1955-1970), and the human radiation experiments (1944-1974). These incidents share corruption in the process of consent.

The informed consent process for participation in clinical studies includes appropriately disclosing all relevant information, ensuring comprehension, voluntariness, and competence. This is an ongoing, bidirectional communication process that empowers people in their autonomy as participants. Understanding unmet needs and identifying effective engagement strategies for communities in Puerto Rico will bridge the health equity gap via culturally tailored materials that facilitate participation and promote ethical conduct of research. This project corresponds to the current US public health mission to address the complexity of health disparities and the need to protect those most at risk, including racial and ethnic minorities.

Our work will advance health equity research and outreach by obtaining clinical research stakeholder feedback and providing practical insights regarding the informed consent process for Puerto Ricans. This project is valuable due to its integration of quantitative and qualitative assessments from a variety of perspectives, levels of expertise, and involvement related to clinical research. Our goals are to increase awareness about gaps in the local informed consent process, to achieve adoption of our proposed guideline, and increase participants’ comprehension of their studies. We envision an enhanced trust in clinical research, increased representation of diverse populations in clinical trials, and improvement of the quality and ethical standards of informed consent processes.

This work is a subprotocol of the Puerto Rico Racial & Ethnic Minority Acceleration Consortium for Health Equity (PR-REACH) IRB #2311166334. This project is unrelated to the attainment of an educational degree by the PI.

LITERATURE REVIEW

Rodríguez-Torres, González-Pérez, and Díaz-Pérez (2021) analyzed thirty reviews covering 753 primary studies –many which included samples of underrepresented groups– and found common barriers and facilitators for participation in clinical trials. They uncovered 20 themes in their synthesis, and at least five domains have factors applicable to the informed consent process. Distrust in the scientists' interests (research rather than wellbeing), concerns of receiving inappropriate therapy, concerns about confidentiality, feeling that they are losing decision-making control, feeling coerced to join, lack of trial knowledge, and complexity of trial details were examples of barriers to participation. Appropriate benefits and incentives were facilitators. Sheridan et al. (2020) also found that emphasizing pain while disclosing information negatively affected participation, while positive framing of potential treatment benefits facilitated it. An informed consent process can be adapted to directly address these elements.

During focus group discussions with their non-Hispanic Black and Hispanic sample, Ross et al. (2024) found recurring mentions of culture and history as obstacles to trust and participation in clinical trials. They developed ten actions for adapting recruitment strategies and study materials targeting their four major themes: mistrust, lack of interest, cultural pressures, and communication & transparency.

Kazembe, Woldeamanuel, and Abay (2024) studied the perspectives of Malawi researchers regarding the informed consent process. Involving third parties, demonstrations, repeated assessments, and providing prior information served as supporting factors for comprehension. Barriers to the informed consent process included language not adapted to the context, length of the process, misconceptions, and the setting. This study is interesting because it represents the opposite side of Ross and colleagues' (2024) work; perspective of the researcher vs perspective of the potential participant.

In 2001, Joffe and colleagues published the Quality of Informed Consent (QuIC) questionnaire. It assesses participants' subjective and objective understanding achieved during the informed consent process of their trial. The QuIC was developed for cancer trials, and it includes language specific to the discipline. Later in 2020, Ruiz de Hoyos et al. expanded and adapted the QuIC without discipline-specific questions. We will build upon this Spanish-validated version in our study. While this instrument is licensed with a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License and available to use without permission, we also contacted the main author via email. To our knowledge, no studies have used this questionnaire.

METHODOLOGY AND STUDY DESIGN

This is a mixed-methods project developed in three phases to assess community feedback across multiple domains regarding the informed consent process in clinical trials in Puerto Rico. To identify potential participants, we will create a database of stakeholders using clinicaltrials.gov (studies from PR; 100 most recent; that are

recruiting; active, completed, and terminated) and local institutions for their contact. We will also use social and physical media to share the survey and invitations.

Phase I

First, we will review Ruiz de Hoyos' et al. (2020) quality of informed consent questionnaire, validated in a Spanish population, with a group of experts in development of qualitative instruments in Puerto Rico for adaptations to a Puerto Rican context (instrument validation). We will use the PR-REACH guidance board to identify at least three experts that will refine the instrument for cultural and language adaptations. Upon instrument refinement completion, we will seek 100 anonymous Puerto Rican adults aged 21 years or older that are currently participating in a clinical trial or a clinical study in Puerto Rico to answer the instrument. The first contact will be through email (link sent via the project's Gmail, consentir.pr@gmail.com), Facebook (via link), Instagram (via link), or through a flyer (via QR code) that will be distributed in bulletin boards at the University of Puerto Rico, Medical Sciences Campus (UPR-MSC). Participants will access the online survey via a Survey Monkey link, which will first describe details of the project. Each participant that completes the survey may provide an alternate contact email for a chance to win one of five $50 cash awards. We will not collect identifying information. We expect the results from the survey and the completed analysis by the end of this Phase.

While the survey data collection is ongoing, we will prepare a topic guide for the next phase: individual interviews and focus groups with clinical research stakeholders (researchers, coordinators, participants, and patient advocacy groups). We will base the guide on Rodríguez-Torres' et al. (2021) domains, which identified barriers and facilitators to participation in clinical research. Experts in qualitative research from the PR-REACH Guidance Board will support the validation of the topic guide. Lastly, the results from the survey will enrich the interview and focus group topic guide by providing additional insight and context. This will promote discussion on the current state of the informed consent process in Puerto Rico and best practices recommendations.

Output: Results from the survey and a topic guide for interviews and focus groups regarding best practices on the informed process for Puerto Ricans

Phase II

Participants in this Phase will be Puerto Rican adults aged 21 years or older that are currently active in clinical research (researchers, coordinators, study participants) or involved in patient/participant advocacy. We will use the www.clinical.trials.gov database to identify clinical research stakeholders and invite at least 10 to a semi-structured 1-hour individual interview and 15 additional people to one 90-minute focus group discussions (three groups composed of five people). The sessions will be possible in online or in-person modality. In-person individual interviews will be held in PR-REACH's office at the UPR-MSC. In-person focus group sessions will be held in a conference room reserved at the UPR-MSC. Individual interview participants will receive a cash incentive of $150. Focus group participants will receive $150 each, and the

sessions will include complimentary beverages and snacks. The PI will schedule and conduct the interviews and the focus group discussions in Spanish only. The content will be recorded, transcribed, and will undergo thematic analysis. After the analysis, we will develop the guidelines.

Output: Guideline detailing best practices recommendations regarding the informed consent process for Puerto Ricans

Phase III

In this phase, we will report on the findings. We will develop abstracts and manuscripts to disseminate our work through conferences and a publication.

Output: Publication of the guidelines for obtaining informed consent from a Puerto Ricans in clinical research

STUDY SUBJECTS

Participants will be recruited from the database, a convenience sample. In Phase II, they will be allocated in either individual interviews or focus groups so that an equal amount of stakeholder types and organization is represented throughout the study. Participants can opt out of the study at any stage without consequence. We will not collect identifying or sensitive information. All data collected, whether that may be subject contact information, demographic or health related information, instruments or results pertaining any protocol directly derived from PR-REACH “master protocol” can be used by PR-REACH’s Administrative, Guidance Board or Research Cores, for the purpose of future studies to be conducted. All physical copies of information regarding participants from any of the three research cores subprotocols will be kept inside PR-REACH’s established office, located at the School of Health Professionals, second floor 236-EPS. The office is locked and only the MPI’s and Core Leads will have access. Digital information will be stored in a cloud-based data storage and only the MPI’s and Core Leads will have access to it as well. The information collected either physically or electronically will be stored for a period of five years; after five years, the physical copies of the collected data will be shredded and disposed of. Information stored on the cloud-based data storage will be permanently deleted.

Risks and Benefits: This study carries minimal risk, but, if necessary, participants can receive a referral to services at the Adult Clinics of the University of Puerto Rico Department of Psychiatry (see letter of support) or the ASSMCA PAS line (#988). Beyond the chance for incentive during Phase I and the incentives in Phase II, participants may not receive any benefit from this study.

VARIABLES

Sociodemographic variables include:

1. Sex
    a. Man
    b. Woman
2. Age group
    a. 18 - 29
    b. 30 - 39
    c. 40 - 49
    d. 50 - 59
    e. 60 or more
3. Education level
    a. Not studied
    b. Elementary school education
    c. High school education
    d. University studies or equivalent
4. Employment status
    a. Student
    b. Internship or practice
    c. Employed
    d. Unemployed
    e. Retired
5. Household income group ($)
    a. Less than 25,000
    b. 25,000 - 50,000
    c. 50,000 - 75,000
    d. 75,000 - 100,000
    e. 100,000 - 150,000
    f. 150,000 - 200,000
    g. More than 200,000
6. Spoken language
7. Previous clinical trial participation and satisfaction

In addition to these, the survey measures the following variables regarding the informed consent process:

1. Part A - Factual knowledge (objective)
    a. Close-ended questions with three levels: Agree, Disagree, Unsure
2. Part B - Perceived knowledge (subjective)
    a. Likert-type questions: 1 “Did not understand anything” to 5 “Understood everything very well”
3. Global comprehension score

In Phase II, we will ask the interviewees and focus group participants:

1. Sex
    a. Man
    b. Woman

2. Age group
    a. 18 - 29
    b. 30 - 39
    c. 40 - 49
    d. 50 - 59
    e. 60 or more
3. Education level
    a. Not studied
    b. Elementary school education
    c. High school education
    d. University studies or equivalent
4. Stakeholder type
    a. Participant
    b. Researcher
    c. Coordinator
    d. Patient advocate

ANALYTIC PLAN

For Phase I, we will extract the descriptive statistics of the survey's sociodemographic data. Item data will be scored by parts (part A and B) and globally and will undergo exploratory inferential analyses, grouped by demographic characteristics. For the interviews and focus groups, we will use thematic synthesis.

Timeline for 2025 (6 months)

Jan - Feb	Mar - May	Jun
IRB preparation and approval	Phases I and II	Phase III

LIMITATIONS

An important limitation to this study is its timeline. It relies on IRB approval by both the UPR-MSC and the FDA. This potentially affects the sample size in Phases I and II of the project, reducing the generalizability.

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