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Addressing ethical challenges in the Genetics Substudy of the National Eye Survey of Trinidad and Tobago (GSNESTT)☆,☆☆

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ABSTRACT

Background: The conduct of international collaborative genomics research raises distinct ethical challenges that require special consideration, especially if conducted in settings that are research-naïve or resource-limited. Although there is considerable literature on these issues, there is a dearth of literature chronicling approaches taken to address these issues in the field. Additionally no previous ethical guidelines have been developed to support similar research in Trinidad and Tobago.

Methods: A literature review was undertaken to identify strategies used to address common ethical issues relevant to human genetics and genomics research in research-naïve or resource-limited settings. Strategies identified were combined with novel approaches to develop a culturally appropriate, multifaceted strategy to address potential challenges in the Genetics Substudy of the National Eye Survey of Trinidad and Tobago (GSNESTT).

Results: Regarding the protection of study participants, we report a decision to exclude children as participants; the use of a Community Engagement and Sensitization Strategy to increase the genetic literacy of the target population; the involvement of local expertise to ensure cultural sensitivity and to address potential comprehension barriers in informed consent; and an audit of the informed consent process to ensure valid consent. Concerning the regulation of the research, we report on ethics approvals from relevant authorities; a Materials Transfer Agreement to guide sample ownership and export; and a Sample Governance Committee to oversee data use and data access. Finally regarding the protection of the interests of scientists from the host country, we report on capacity building efforts to ensure that local scientists have access to data collected through the project and appropriate recognition of their contributions in future publications.

Conclusion: This paper outlines an ethical framework for the conduct of population-based genetics and genomics research in Trinidad and Tobago; highlights common issues arising in the field and strategies to address these.

1. Introduction

It is well documented that there are a host of ethical issues associated with the conduct of human genetics and genomics research (HGR). Typically these issues are related to concerns regarding informed consent, privacy of research participants, return of results and incidental findings, data storage and data sharing (de Vries et al., 2011; Kaye et al., 2010; Wright et al., 2013). Many ethical issues associated with

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HGR are particularly heightened when these projects are international collaborations involving research-naïve or resource-limited settings (de Vries et al., 2011).

In these settings, there is an overall concern about the lack of capacity of the host countries to conduct and lead the research themselves as well as the lack of well-trained ethics review committees and regulatory agencies (Chanda-Kapata et al., 2015; Roach, 2015). There are also corresponding concerns about the need for project designs to take into account cultural beliefs and practices of the host community, the degree of exposure (and education) of the community with respect to genetics and the true potential of the project to yield benefits to the host country (Ramsay et al., 2014; de Vries et al., 2015). Issues related to the appropriateness of informed consent models, maintaining the privacy and confidentiality of study participants, and disclosure of findings including incidental findings and obligations to family members take center stage (McGuire and Beskow, 2010; Kaye et al., 2010; Ramsay et al., 2014; de Vries et al., 2015; Chanda-Kapata et al., 2015). Additionally, given the social and economic contexts of many of the target populations there are underlying concerns about potential stigmatization and discrimination, especially since most countries lack legislation to protect against this type of harm (WHO, 2002; Foster and Sharp, 2006). Other key issues in these settings include the sharing of samples and data across different jurisdictions (Chanda-Kapata et al., 2015).

These ethical issues have been categorized into three main classes: protecting the interests of research populations; regulating human genomics research; and protecting the interests of scientists in the developing world (de Vries et al., 2011). While the literature contains extensive discussion of these ethical issues, there are fewer articles chronicling approaches taken to address these issues in the field. Additionally, articles providing information about the approaches used in the field have been limited to research conducted on the African continent. There is a paucity of literature specific to the Caribbean Basin. This article attempts to bridge this gap by reporting on measures taken to address key ethical challenges in the Genetics Substudy of the National Eye Survey of Trinidad and Tobago (GSNESTT).

1.1. The context and rationale for a National Eye Survey of Trinidad and Tobago (NESTT)

An estimated 32.4 million people worldwide are blind and 191 million are moderately or severely visually impaired (Bourne et al., 2013). Given the high prevalence of numerous risk factors for eye disease and vision loss in the population (Chadee et al., 2013; Cawich et al., 2014; Pan American Health Organisation, 2013), in particular diabetes mellitus, local eye care professionals and local government thought it was necessary to gather data on the prevalence, causes and risk factors of vision loss in Trinidad and Tobago (TT). As such the National Eye Survey of Trinidad and Tobago (NESTT) was conceptualized (see Box 1). The aim of the study was to generate an evidence base to inform policies and health service development to reduce the burden of avoidable vision loss in the population. This study was funded primarily by the local Ministry of Health (MOH), and was delivered through an academic collaboration between the University of the West Indies (UWI) and Anglia Ruskin University (ARU) in the United Kingdom.

1.2. The rationale behind the Genetics Substudy of the NESTT (GSNESTT)

In recent years, multiple studies have explored the genetic epidemiology of eye disease and have greatly advanced understanding of how and why diseases develop in different populations (Li et al., 2015; Bailey et al., 2016). Given the reportedly high burden of eye disease in Trinidad and Tobago, coupled with the supporting scientific literature highlighting the presence of genetic risk factors in populations with high burdens of eye disease, the study team felt that the data collected in the main study would be inadequate to investigate genetic and environmental factors contributing to the reportedly high burden of eye disease in Trinidad and Tobago.

Box 1
Description of the National Eye Survey of Trinidad and Tobago (NESTT).

The National Eye Survey of Trinidad and Tobago (NESTT) (September 2013–November 2014) was a nationally-representative, population based epidemiological survey to determine the prevalence, causes and risk factors for vision loss in the population aged 5 years and above in Trinidad and Tobago. Randomized multistage sampling, using probability proportionate to size methods, was used to select approximately 10,000 individuals in 120 geographical clusters. Participants had a basic vision assessment and interview in their communities. Everyone aged 40 years and above, and those aged 5 to 39 years with vision impairment or diabetes mellitus, were invited for comprehensive medical and ophthalmic assessment in regional clinics. The clinical examination included ocular photography, biometry and optical coherence tomography of the anterior and posterior segments.

Further considering that the majority of recent studies on the genetic epidemiology of eye diseases have focused on Caucasian and Asian populations, and it was unclear whether the population of TT possessed a unique set of genetic variants, which might influence disease susceptibility and the effectiveness of specific treatments. To address these concerns, the Genetics Substudy of NESTT (GSNESTT) was designed (see Box 2).

1.3. The rationale for developing an ethical framework for GSNESTT

Trinidad and Tobago (TT) is the most industrialized nation in the Caribbean, with low unemployment rates and high literacy rates. It was removed from the OECD list of developing countries in 2011, and in 2015 the nation was ranked as a "High Income" country by the World Bank. Despite these positive socioeconomic indicators, several considerations relating to the sociocultural context of TT made the ethical issues associated with the GSNESTT worthy of special attention.

Firstly, the GSNESTT was the first genetics/genomics study conducted in TT that included a nationally-representative population sample. The stakeholders (academic and government) were therefore conscious of the fact that this study would impact the landscape for other similar studies in the country. Specifically, it was acknowledged that the way

Box 2
Description of the Genetics Substudy of the NESTT (GSNESTT).

The Genetics Substudy of the NESTT (GSNESTT) (August 2014–June 2015) aimed to create a research database of clinically-well characterized individuals to investigate genetic and environmental factors associated with vision loss and blindness in Trinidad and Tobago, including cardiovascular diseases. The GSNESTT involved the collection of saliva samples from volunteers, aged 18 years old and above, who completed a comprehensive ophthalmic and medical assessment in the main NESTT epidemiological survey. Samples were transported from the field for temporary storage at the University of the West Indies, and were shipped to Duke University Biobank in the USA for DNA extraction and storage. Future research utilizing this research database will include Genome Wide Association Studies.

in which the study was perceived by the public could impact public trust towards genetics or genomics research; that the tools and procedures created for the GSNESTT could serve as a benchmark for similar studies; and that the knowledge gained from this study could inform policies to regulate future human genetics research in Trinidad and Tobago.

Secondly, a major concern was the paucity of data on genetic literacy and attitudes towards genetic and genomic research of the general population in TT. There was also limited data on the capacity of local research ethics committees to adequately evaluate genetics and genomics research proposals. This meant that cultural nuances that may have affected participant participation in the GSNESTT were unclear and questions about the capacity of the participants to comprehend the implications of their participation in the study were raised.

Thirdly, there was an absence of dedicated bioethics (or research ethics) training programs at the local universities and a lack of legislation in the country to regulate HGR or use of genetic data. Furthermore, NESTT planned to transfer genetic data abroad on account of inadequate capacity for long term secure storage of DNA in country, and a lack of automated facilities for DNA extraction and whole genome analysis. Taken together these raised issues about the ability of TT to protect participants from possible discrimination as well as regulate the secondary use of participant data once they left local shores.

A final consideration was the fact that the study was funded by the local government. Stakeholders felt that the use of public funding implied an expectation of direct and immediate benefit to the population. This was a source of major concern as the team understood that the benefits of GSNESTT may not be immediately apparent. Therefore, at the outset it was decided that since the study was publicly funded and the country had more pressing public health concerns, budget allowance would only be made for the collection of tissue samples. To facilitate storage and DNA extraction, an academic collaboration was established with a highly reputed genomics center in the United States at no cost, and the team agreed that external grants would be sought for genomic analyses. Also, in light of the logistical issues of collecting blood samples, saliva was chosen as the preferred source of genetic information.

Given these observations, the team recognized that TT may be considered research-naive with regard to genetics and genomics research and therefore it was necessary to build into the GSNESTT mechanisms to address possible ethical challenges that could be faced in the field. As a result, a review of the literature was conducted to identify strategies and practices commonly employed by other similar studies.

2. Methods

A review of the literature on ethical issues associated with genetics and genomics research in developing countries, research-naïve or resource-limited settings published up to October 31, 2013 was conducted using Pubmed (National Library of Medicine). The search was constructed to identify primary studies and 'experiences' on approaches used to address ethical issues in international collaborative HGR projects. Articles providing an overview on specific ethical issues were accessed as long as they also included practical recommendations. Thus, although there is a wealth of information on ethical issues related to genetics and genomics research, many published papers were not considered relevant for this analysis. Fig. 1 outlines the process of selection of articles for this literature review. Through this process, eleven (11) articles of relevance to the development of an ethical framework in this study were identified (see Table 1).

The process of data extraction involved a critical review of the selected articles to identify the following information: type of primary study; ethical issues identified; strategies and rationale underlying strategies used to address the ethical challenges. Particular attention was given to discussions related to issues of informed consent, secondary data use, transfer of data across borders, and the treatment of incidental findings. Using the tripartite classification for ethical issues in human genomics research conducted in less developed countries (de Vries et al., 2011), the main ethical issues identified in the literature were grouped into the following categories: i) protecting the interests of research populations; ii) regulating human genomics research; and iii) protecting the interests of scientists in the developing world. The strategies presented in the articles addressing ethical issues in these areas were identified and tabulated (see Table 2).

Using strategies reported from other studies or suggested in the literature, the study team developed a comprehensive ethical approach to guide the GSNESTT in the following eight key areas: 1) fair selection of study participants; 2) community engagement and sensitization; 3) ensuring valid informed consent; 4) assuring the quality of the informed consent process; 5) acquiring necessary ethics approvals; 6) regulating the transfer of data across borders; 7) regulating the secondary use of data; and 8) capacity-building in TT. Finally, the GSNESTT ethical framework was assessed to ensure adherence to general international guidelines on the ethical conduct of human subjects' research (see Table 3).

3. Results

3.1. Developing an ethical framework to guide the GSNESTT

Drawing from all the literature, the following multifaceted strategy was developed to guide the GSNESTT.

3.1.1. Protecting the interests of research populations

3.1.1.1. Fair selection of study participants. Recruitment for NESTT utilized multi-stage, randomized, cluster sampling, with probability proportionate to size methods. This gave each person aged 5 years and above in the non-institutionalized population of TT an equal chance of being selected for inclusion in the study. At the outset, the study team decided that although participation by children had the potential to offer additional advances in understanding developmental eye conditions, the GSNESTT would not include children as participants. Despite the ethical approaches presented in the literature informing the inclusion of children in HGR (de Vries et al., 2011), the research team recognized that this would introduce complex ethical issues, particularly with respect to informed consent.

3.1.1.2. Community engagement and sensitization. Protecting the interests of research participants through the engagement of the community was paramount. Consistent with the literature, key stakeholders were identified and engaged. These included professional societies, advocacy and patient groups, governmental and non-governmental organizations, and academic institutions, many of whom had been engaged prior to the start of the main epidemiological study. Careful consideration was also taken to develop a Community Engagement and Sensitization Strategy (CESS) to provide essential guidance for the engagement and sensitization of stakeholders involved in the GSNESTT.

Under the guidance of the Communications Department in the Ministry of Health, an official soft launch was held for the GSNESTT, followed by a major media campaign – both approaches mentioned in Chokshi et al. (2007). Given the lack of data regarding the genetic literacy of the population of TT, a key element of the media campaign was to increase basic education in genetics, and raise awareness about the purpose and nature of the study. Articles were published in the local newspapers and the university's newsletter providing basic information on genetic terminologies and concepts, as well as highlighting major ethical issues in genetics/genomics research (Carrington and Roach, 2014; Roach, 2014). Radio and television interviews were held with key members of the NESTT research team, in which the study was introduced and basic information about genetics and genetics/genomics research discussed in relation to eye disease. Additionally a Facebook page was used to provide engagement via social media. A scientific forum on a

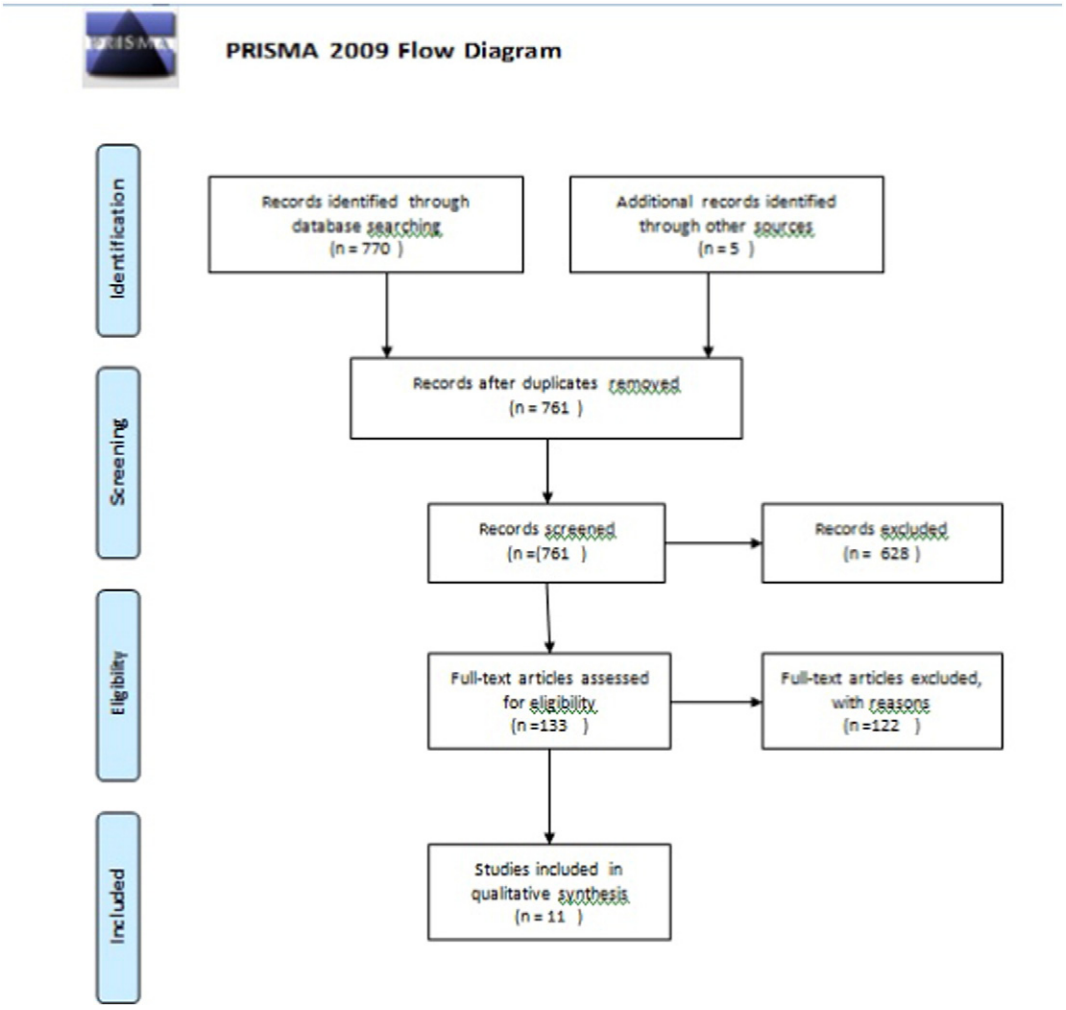

Fig. 1. Process of selection of articles for the development of the GSNESTT Framework.

related topic was also organized to improve genetic education, and to reduce any fear and mistrust in the scientific community and general population.

In line with the reports by de Vries et al. (2011) and Tindana et al. (2012), the engagement activities were shaped by the characteristics of the target population. The communities targeted were highly diverse,

Table 1
Identified articles including approaches to address ethical challenges associated with genetics and genomics research in developing countries or resourced strapped nations.

Identified articles	Justification for inclusion
Caulfield T, McGuire AL, Cho M, et al. Research Ethics Recommendations for Whole-Genome Research: Consensus Statement. PLoS Biology. 2008;6(3):e73.	Overview with recommendations
Chokshi DA, Parker M, Kwiatkowski DP. Data sharing and intellectual property in a genomic epidemiology network: policies for large-scale research collaboration. Bulletin of the World health Organization. 2006 May;84(5):382–7.	Practical Experience MalariaGEN
Chokshi DA, Thera MA, Parker M, et al. Valid Consent for Genomic Epidemiology in Developing Countries. PLoS Medicine. 2007;4(4):e95.	Overview practical experiences various studies Africa
De Vries J, Bull SJ, Doumbo O, et al. Ethical issues in human genomics research in developing countries. BMC Medical Ethics. 2011;12:5.	Practical Experience MalariaGEN
Kaye J, Boddington P, de Vries J, Hawkins N, Melham K. Ethical implications of the use of whole genome methods in medical research. European Journal of Human Genetics. 2010;18(4):398–403.	Overview with recommendations
McGuire AL, Beskow LM. Informed Consent in Genomics and Genetic research. Annual review of genomics and human genetics. 2010;11:361–381.	Overview with recommendations
McGuire AL, Caulfield T, Cho MK. Research ethics and the challenge of whole-genome sequencing. Nature reviews Genetics. 2008;9(2):152–156.	Overview with recommendations
Parker M, Bull SJ, de Vries J, Agbenyega T, Doumbo OK, Kwiatkowski DP (2009) Ethical Data Release in Genome-Wide Association Studies in Developing Countries. PLoS Med 6(11): e1000143.	Practical Experience MalariaGEN
Staunton C and Moodley K. Challenges in biobank governance in Sub-Saharan Africa. BMC Medical Ethics 2013, 14:35.	Overview H3Africa
Tindana P, Bull S, Amenga-Etego L, et al. Seeking consent to genetic and genomic research in a rural Ghanaian setting: A qualitative study of the MalariaGEN experience. BMC Medical Ethics. 2012;13:15.	Practical Experience MalariaGEN
Wright GE, Koornhof PG, Adeyemo AA, Tiffin N. Ethical and legal implications of whole genome and whole exome sequencing in African populations. BMC Medical Ethics. 2013;14:21.	Practical Experience H3Africa Consortium

Table 2
Approaches used to address ethical issues in genomics research the field.

Selected approaches used in the field to address ethical challenges associated with international collaborative genetics and genomics research		
ETHICAL ISSUE	**APPROACH**	**REFERENCE**
A. Protecting the interests of research Participants		
1) Fair selection of study participants		
i. Issues related to involvement of children	Development of specific protocols for children eg assess competence on case by case basis	Choksi et al (2007) de Vries et al (2011)
2) Community Engagement and Sensitization		
i. Community Engagement	Model of engagement consistent with community processes Ad hoc community engagement initiatives Community Meetings Community Advisory Groups Official ceremony	Tindana et al (2012) de Vries et al (2011) Tindana et al (2012) Wright et al (2013) Choksi et al (2007)
ii. Improvement of genetic literacy/ community education in genetics	Tailored to local setting eg videos, announcements, audio etc	Choksi et al (2007)
Ensuring valid informed consent		
i. Participant comprehension: linguistic and cultural barriers	Using local language or culturally relevant descriptive to explain complex concepts like "genetics" and "genomics"	Choksi et al (2007) de Vries et al (2011) Wright et al (2013) Tindana et al (2012) McGuire et al (2008)
ii. Informing participant about complex issues, eg: potential loss of identity, incidental findings and group stigmatization	Collaborative approach towards development of informed consent document. Candid discussion in consenting process and Inclusion in consent form Need for legislation/relevant guiding policy e.g. return of results policy	de Vries et al (2011) Choksi et al (2007) Caufield et al (2008) Wright et al (2013) Tindana et al (2012) McGuire et al (2010) McGuire et al (2008) Kaye et al (2010) Wright et al (2013)
iii. Challenges in administering consent	Training of field workers and discussion of possible different scenarios eg emergency situations	de Vries et al (2011) Tindana et al (2012)
iv. Reducing inducement that may arise from offering medical care	Repeat during study (and assess) that provision of care is not contingent on participation	Choksi et al (2007)
Assuring the quality of the informed consent process		
i. Ensuring validity/assuring quality of consent	Assessments in the field	Tindana et al (2012)
B. **Regulating human genomics research**		
Regulating the transfer of samples and data across borders		
i. Cross border data issuesrelating to Eg transfer of samples and privacy and confidentiality of data	Use of a Materials Transfer Agreement Need to establish legislation/policy	de Vries et al (2011) Wright et al (2013) Staunton et al (2013) McGuire et al (2008) Caufield et al (2008)

Regulating the secondary use of samples and data		
ii. Secondary use of samples in a manner consistent with participants' consent (data access) or sharing of data in general for research purposes	Governance Structure eg. Data Access Committee or data sharing/access policy	Choksi et al (2006) Parker et al (2009) Caufield et al (2008) Wright et al (2013) Kaye et al (2010)
	Mechanism to facilitate communicat ion/data release between researchers and participants eg online	McGuire et al (2010)
	Certificates of Confidentiality	McGuire et al (2010)
Acquiring necessary ethics Approvals		
iii. Ethics review	Ethics approvals from all partners	Caufield et al (2008) de Vries et al (2011) Wright et al (2013)
C. **Capacity building of local community**		
Capacity building in TT		
Building capacity of local researchers	Training of local researchers in analysis of genomic data	de Vries et al (2011)
	Workshops for local RECs/IRBs	Wright et al (2013)
	Development of a software to allow for remote analysis of genomic data	de Vries et al (2011)
	PhD. Studentship to investigate ethical issues	de Vries et al (2011)
	Policies/relationships guiding how data is released	Choksi et al (2006)

ranging from wealthy suburban neighborhoods, with established street signs and extensive postal systems that were easily accessible, to extremely rural and highly impoverished areas, with houses that were not present on town maps, a corresponding post system that was not as structured, and terrain that at times was accessible only via footpaths. As a result, a more personal, labor and resource intensive strategy of participant engagement was devised. Further, based on the premise that informed consent starts at the first moment of contact with potential participants, participant engagement strategies were designed to uphold the voluntariness of informed consent as well as reduce any possibility of undue influence.

All potential target areas were assessed individually and engagement protocols were reviewed and tailored to suit the specific community. Some people were recruited at the time they attended clinic for their eye exam, and under these circumstances care was taken to ensure that the participants did not feel pressure to participate (Chokshi et al., 2007). A majority of participants were recontacted afterwards and invited to participate in the GSNESTT. The method for recontact involved using a telephone script as a guide, and calling each potential participant. Once potential participants indicated that they were not interested in learning more about the study, they were not contacted again. Following telephone contact, the team visited communities wearing NESTT uniforms and a blow horn was used to announce the days that the study team would be visiting. A brochure which outlined the purpose of the Genetics substudy, the risks and benefits, and procedures involved, was left with each household and participants were given the consent form to review.

3.1.1.3. Ensuring valid informed consent. Recognizing the value of a collaborative approach to developing the informed consent document (de Vries et al., 2011), the GSNESTT informed consent form was developed in an iterative fashion with input from stakeholders including researchers at the collaborating institutions, and in accordance with international best practice. With the assistance of a local geneticist trained in research ethics and the conduct of genetics research in underrepresented communities, a genetics team was trained specifically to obtain informed consent and collect samples at the individual level. Training included using local analogies to explain complex terms; collecting consent in various settings – from the clinic to under a tree in a yard; and discussing complex ethical issues like incidental findings, recontact, biobanking, and the limits of privacy and confidentiality (Chokshi et al., 2007; de Vries et al., 2011; Wright et al., 2013; Tindana et al., 2012; McGuire et al., 2008).

Although not discussed in the literature, the GSNESTT team enlisted a local holding a Masters level degree in clinical psychology as an added safeguard to address issues related to the comprehension level of potential participants. This individual, who also received the study specific training alongside the team, was selected to lead the GSNESTT consenting group and helped to ensure that the team recognized verbal and nonverbal cues indicating poor comprehension, possible

Table 3
Areas of the CIOMS Guidelines addressed in the GSNESTT.

CIOMS Guideline	Addressed	Not Addressed	Not applicable
Guideline 1: Ethical justification and scientific validity of biomedical research involving human beings	✓		
Guideline 2: Ethical review committees	✓		
Guideline 3: Ethical review of externally sponsored research	✓		
Guideline 4: Individual informed consent	✓		
Guideline 5: Obtaining informed consent: Essential information for prospective research subjects	✓		
Guideline 6: Obtaining informed consent: Obligations of sponsors and investigators	✓		
Guideline 7: Inducement to participate	✓		
Guideline 8: Benefits and risks of study participation	✓		
Guideline 9: Special limitations on risk when research involves individuals who are not capable of giving informed consent	✓		
Guideline 10: Research in populations and communities with limited resources	✓		
Guideline 11: Choice of control in clinical trials			✓
Guideline 12: Equitable distribution of burdens and benefits in the selection of groups of subjects in research	✓		
Guideline 13: Research involving vulnerable persons	✓		
Guideline 14: Research involving children	✓		
Guideline 15: Research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent	✓		
Guideline 16: Women as research subjects	✓		
Guideline 17: Pregnant women as research participants.	✓		
Guideline 18: Safeguarding confidentiality	✓		
Guideline 19: Right of injured subjects to treatment and compensation			✓
Guideline 20: Strengthening capacity for ethical and scientific review and biomedical research	✓		
Guideline 21: Ethical obligation of external sponsors to provide health-care services	✓		

therapeutic misconceptions, and other indications that potential participants felt unduly influenced or coerced to participate in the study.

3.1.1.4. Assuring the quality of the informed consent process. Tindana et al. (2012) includes discussion on assuring the quality of the informed consent process. The GSNESTT addressed this issue by undertaking an audit of the informed consent process during the pilot phase of the study. For the purpose of this audit a transdisciplinary team of observers was assembled. This included members of the NESTT Sample Governance Committee and NESTT Steering Committee. In addition, to ensure transparency and independent review, other stakeholders were invited, including a representative from the Ministry of Health, a representative of the inter-religious organization, and a well-established bioethicist from a regional public health agency.

The audit team visited the survey team in the clinic, and was asked to document, on audit proforma, whether ethical standards and requirements were being met, and whether the procedures employed in the field upheld best practices in the area, and were consistent with those set out in the approved study protocols. Specifically, the team was asked to ensure that: a) participants were being consented adequately and free of coercion; b) participants comprehended what they were consenting to; c) participants' (research subject) rights were being upheld; and d) participant samples were being appropriately collected. They were also asked to document their observations regarding steps taken to ensure participant privacy and confidentiality, and the environment in which the study was taking place. The audit team submitted a report, which indicated that no direct breach of participants' rights was observed and that participants' samples appeared to be appropriately collected. However, areas for improvement were also noted, which were submitted in the form of recommendations to the NESTT Steering Committee. Briefly the main change included giving the study participants more time to process the details and implications of the study before consent was taken, and this change was adopted by the survey team.

3.1.2. Regulating human genomics research

3.1.2.1. Acquiring necessary ethics approvals. From an ethical perspective, perhaps the most challenging aspect of this study was ensuring that the research was well-regulated given the absence of local policy. To begin,

the NESTT Steering Committee and funders recognized that it was essential for the Genetics substudy to receive ethics approval from the collaborating academic institutions and the local Ministry of Health – an approach consistent with Caulfield et al. (2008), de Vries et al. (2011), and Wright et al. (2013). In total, the study received ethics approvals from 4 ethics committees located in 3 different countries, each with their own standards and list of requirements. Notwithstanding the procedural delays and logistical challenges, meeting the requirements of these multiple committees ensured that the proposed study met both local and international standards in research ethics.

3.1.2.2. Regulating transfer of samples and data across borders. Additionally, it was decided that a Materials Transfer Agreement (MTA) was critical to regulate the transfer of samples abroad (de Vries et al., 2011; Wright et al., 2013). As a result, a three-way MTA was developed and signed by the three collaborating universities: The University of the West Indies, Duke University and Anglia Ruskin University. Key areas addressed in this MTA included the purpose of transferring the materials to Duke University and limits of use, applicable laws regulating the handling of the samples and privacy and confidentiality of data.

3.1.2.3. Regulating secondary use of data. A Sample Governance Committee (SGC) was established to oversee the future use of, and access to, DNA extracted from samples collected in this study (Chokshi et al., 2006; Parker et al., 2009; Caulfield et al., 2008; Wright et al., 2013; Kaye et al., 2010). This diverse team comprised members of all three academic institutions, the Ministry of Health, and independent local scientists. The principal duties of the SGC included advising on secondary uses and analyses for the purposes of academic outputs.

An important role of the SGC was to ensure sample use in compliance with the permissions received from the participants. To facilitate this, a coded database was created containing information from consent forms regarding varying limits of use that were agreed upon individually by each participant. Specifically, this database contained information on whether permission was granted for DNA to be used for only NESTT study research; for other research involving eye and cardiovascular disease; or for inclusion in the Duke biobank, for general biomedical research. The database also contained other information about participant preference regarding 1) being informed about incidental findings; and 2) being re-contacted for future studies.

3.1.3. Protecting the interests of scientists in the host country

3.1.3.1. Capacity building in TT. Whenever international collaborative research is conducted in lesser developed countries there is always a concern that the interests of scientists in the host country should be protected. To account for this, the GSNESTT included several efforts to build capacity in the host country. For example, all local members of the study team were provided with basic education in genetics and trained to convey genetic information and identify ethical, legal and social issues associated with genetics/genomics research.

In addition several local professionals were included in the GSNESTT. Specifically, a local human geneticist was employed as a consultant to the study and an individual trained in clinical psychology was employed to lead consenting efforts. Local scientists were selected to lead subcommittees, including the Sample Governance Committee. It was also agreed that local collaborating investigators would co-author publications arising from the study. Inspired partly by the GSNESTT, an article was published highlighting the need to build capacity for genetics and genomics research in TT and the wider region (Roach et al., 2015). Provision was also made for local scientists, through application to the Sample Governance Committee, to have access to the de-identified data generated through the GSNESTT for research.

Building on the work of the GSNESTT project, the local geneticist was hired by the local university to build a research ethics curriculum, train healthcare students in the ethical, legal and social implications of genetics research, and serve on the University's research ethics committee. This expanded the curriculum and added expertise to the research ethics committee at the university, and also reflected the university's recognition of the importance of building capacity in this area.

3.2. Consistency with international guidelines

A summary of the areas of the International Ethical Guidelines for Biomedical Research Involving Human Subjects herein referred to as CIOMS (CIOMS, 2002) that was covered in the GSNESTT study is presented in Table 3. Briefly, 19 of the 21 ethical guidelines included in the CIOMS were considered. Of the remaining 2 guidelines, "Guideline 11: Choice of Clinical Trials", was not considered because the GSNESTT was not a clinical trial; and "Guideline 19: Right of injured subjects to treatment and compensation", was not considered because the donation of a saliva sample for the GSNESTT was considered to confer minimal risk of causing injury. It must also be noted that in TT, public health care that is free at the point of delivery is provided to all citizens by the Ministry of Health who sponsored the research.

4. Discussion

In summary, eight key areas of concern were identified as requiring special attention for human genetics and genomics research in TT: 1) fair selection of study participants, 2) community engagement and sensitization; 3) ensuring valid informed consent; 4) assuring the quality of the informed consent process; 5) acquiring necessary ethics approvals; 6) regulating the transfer of data across borders; 7) regulating the secondary use of data; and 8) Capacity-building in TT. Using strategies identified in the literature, combined with novel approaches and responsiveness to challenges encountered in the field, we were able to develop a culturally appropriate, multifaceted strategy to address potential ethical challenges in the GSNESTT.

Specifically, in addressing issues of fair selection of study participants we decided to exclude children as participants. Related to issues of fair selection, community engagement and sensitization was viewed as crucial to recruiting participants who may be research-naïve. As a result an extensive community engagement and sensitization plan was developed which took into account the culture and diversity of communities targeted. To ensure valid informed consent, several strategies were used including the involvement of local expertise and training of the consent team. Issues related to comprehension were further addressed by involving an individual trained in clinical psychology as a member of the consenting team. Additionally, the quality of the informed consent process was assured through an independent audit. The study acquired ethics approvals from all institutions involved and the local Ministry of Health, and issues related to the transfer and secondary use of samples and data were addressed through a legally binding Materials Transfer Agreement and a Sample Governance Committee, respectively. Finally as all international collaborative research projects should seek to build capacity in the host country, several mechanisms were put in place to protect the interests of scientists in TT.

4.1. Unexpected challenges

Every research project faces unexpected challenges. One unexpected challenge was the time required to develop and implement this ethical framework, and to receive the necessary ethics committee approvals. This resulted in a delayed start of the GSNESTT relative to the start of the epidemiological survey. In the end, this delay affected the GSNESTT participant recruitment process. A second unexpected challenge was the development of a negative public campaign, launched by stakeholders opposed to the genomics research project. This aimed to dissuade the population from participating in both the main epidemiological and genetics studies. The campaign utilized newspaper

advertisements, letters to professional societies and other stakeholders, including high level government officials and administrators at all the academic institutions involved. This campaign questioned the use of public funds, the ethical framework used for the study, the involvement of children in the study, and the creation of a biobank with storage of tissue abroad - the same ethical issues that were taken into consideration in the development of the above plan. To date it is unclear what effect, if any, this campaign may have had on the general perception of the ethical acceptability of the GSNESTT.

5. Conclusion

The diversity of political, sociocultural and infrastructural factors that exist in each country may impede the establishment of a single ethical approach to international collaborative genetics/genomics research that will be effective in all contexts. However, as the GSNESTT experience proves, drawing on the published experiences of other projects, it is possible to identify key areas in HGR that require special attention and then integrate several previously tested mechanisms to address many ethical issues that may arise. Novel approaches integrated into the GSNESTT include the use of a local trained in clinical psychology to lead the informed consent process, and developing an audit protocol to assure the quality and validity of the informed consent process. It is critical that any framework developed also addresses key areas outlined in international guidelines like the CIOMS. Care must also be taken at every step to ensure that study protocols are sensitive to the culture and terrain of each community or subgroup targeted within a country. Community engagement and recruitment is a resource and labor-intensive aspect of the project, and required creativity and flexibility to achieve successful implementation.

Our experience suggests that for research projects involving genetics to be successful, ethical issues must be integrated into the design and implementation of the project. The value and importance of identifying and meaningfully engaging with all interested stakeholders, prior to a major project, and throughout its evolution, cannot be overstated. Failure to do so can lead to costly delays and may potentially undermine the viability of the research. Building on the GSNESTT, we recommend that further investment is made to develop community education in genetics and the implications of genetics research in Trinidad and Tobago.

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