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Genetic material should be routinely collected in clinical vaccine trials – High consent rates can be achieved across all age groups

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ABSTRACT

Background: Genomic and transcriptomic studies underpin much investigation in biology and should be included routinely in clinical trials such as vaccine studies to provide new insight into the development of immunity and the genetic basis for adverse reactions. Interest in collecting and storing genetic material for subsequent high-throughput meta-analyses has increased substantially in recent years. Participants in clinical trials represent an important and invaluable source of clinical material and data.
Methods: Here, the experience of a single center in obtaining informed consent for the collection and long-term storage of genetic material from children, adolescents and adults, involved in clinical vaccine trials is presented and discussed.
Results: In 11 completed vaccine studies involving almost 3000 individuals, high rates of consent (in excess of 96%) for biobanking and future genetic testing were obtained. Rates were high for participants from all age groups; however, there was a significant increase toward greater uptake by older study participants.
Conclusions: These high acceptance rates demonstrate that participants (and parents of young children) in vaccine studies are willing to consent and engage in genetic research, which provides support for routinely collecting genetic material in research involving healthy participants such as clinical vaccine trials.

1. Introduction

Randomized controlled trials are regarded as the gold standard for clinical research; however data from a single study in isolation may be insufficient for answering important research questions. In particular, genetic studies require large datasets to establish associations between host genetic factors and clinically relevant phenotypic traits, such as prediction of disease susceptibility or likely response to medical interventions. Gathering biological, in this case genetic material (e.g. DNA or RNA), in a biobank repository for future pooled investigation of heterogeneous populations sharing a common characteristic (e.g. vaccine receipt), may help to identify important genetic associations and hence, for example, individuals at risk of specific diseases or more suited to a particular treatment modality [1–3]. In addition, such studies may help to identify associations between genotype and immunological "behavior" potentially leading to new insights into immunobiological or molecular processes or the development of novel biomarkers [4,5].

"Genetic testing" has long been a source of controversy, in part due to the complexities of international legislation. Since the completion of the Human Genome Project in 2003 [6], different national and regional authorities have instituted an array of legislation, in part due to public fears regarding the use and/or misuse of genetic data [7]. In the UK, collection, storage, distribution and use of human biological material including DNA and serum are excluded from the definition of "relevant material" as they do not consist of, or include, human cells, as defined in the Human Tissue Act 2004 and are therefore exempt from requiring a HTA license [8]. While appropriate consent is generally accepted practice prior to genetic testing of any sort [9–11] and a legal requirement in the UK [12], specific issues have been raised regarding the need for consent for storage of biological material [13]. Specifically, the use of pediatric samples for genetic research remains a controversial and particularly emotive issue [14–17]. Infants and children are unable to provide informed consent [18], and there are clear moral issues for parents/guardians providing consent on behalf of their offspring. Pediatrics samples, however, offer an important resource of information about the development and maturation

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Please note that your child can still participate in this study whether or not you agree to the next statements:

I agree that blood from my child may be used for analysis of genetic factors related to vaccine responses. |_____|

I agree that any remaining blood from my child may be stored and used in future research related to vaccines and infectious diseases (with the exception of Human Immunodeficiency Virus [HIV]). |_____|

Fig. 1. Example of the additional boxes in a consent form of a pediatric vaccine trial used to obtain consent for genetic testing and for storage of serum.

of immunobiological processes, such as responses to vaccination [19]. Whether the consent rate for genetic testing and biobank storage of material among pediatric populations is the same as that among older adults is currently unknown.

The Oxford Vaccine Group has conducted a large number of clinical vaccine trials in the last 10 years, enrolling several thousand study participants. Since 2004, DNA samples and serum from study participants have been deposited into a biobank, which continues to provide a unique resource of study material. In this report we examined the rates of participant consent for genetic testing and storage observed in clinical trials conducted across various age groups.

2. Methods

A retrospective descriptive analysis was performed of all studies that had completed enrolment by April 2011 and in which consent for genetic testing and biobank storage was documented. Data were collected from participant case report forms, stored/archived original consent forms and secure electronic databases. Rates of consent in relation to age and gender of study participants were examined in addition to age of the consenting parent/guardian in pediatric studies when available.

2.1. Consent for genetic research

At enrolment into each study, the participant or a legal guardian of the participant provided written informed consent as part of a process conducted by trained study doctors or nurses. Where appropriate, assent was obtained from the participant. Separate check boxes were used to obtain consent for storage of serum and for genetic testing to identify factors related to vaccine responses (Fig. 1). Study participants were informed that they would not be given individual genetic results, as analyses would be performed on samples unlinked from personal identifiable data (PID). Double-coded sample labeling ensures that all samples and PID remain confidential, with linking information only held in a secure database independent from the research group. During the consent process participants or parents of pediatric participants are notified that, if they changed their minds and no longer wanted biological samples to be retained, they could request sample destruction without it affecting their participation in the study. In all studies, DNA extraction was performed using blood clots remaining after centrifugation of whole blood; no cell lines were generated. DNA samples were subsequently labeled with a unique biobank number generated by an independent study statistician.

3. Results

In total, 2998 individuals participating in 11 studies were included in the analysis. Five out of 11 studies were multicentered involving 2–8 other sites; 6/11 were single center studies conducted in Oxford. Only data from participants recruited at the Oxford study site were analyzed for the purposes of this study (see Supplementary Table 1 for details). The mean participant age at enrolment in individual studies ranged from 2 months to 59 years and 1545/2998 (51.5%) study participants were male (see Table 1). Only 45/2998 study participants or their responsible parent/guardian, refused consent for genetic testing to be performed corresponding to 1.5% of all study participants approached. There was a significant increase ($p < 0.0001$, Chi-square test) in the proportion providing consent for genetic testing among older study participants: 100% in both adult studies performed (Fig. 2). Within each study, neither the age of the participant nor a child participant's parents' age influenced the decision about biobank storage and hence future genetic testing, with the exception of child study 3 (see Table 1). In this study, in which children aged 6 months to 12 years were recruited, the mean age of participants whose parents/guardians did not provide consent was 2.7 years ($n = 5$) compared with 4.3 years among those who did provide consent ($n = 271$, $p =$ NS, two-sided Mann–Whitney test). Participant gender did not influence the decision to provide consent for genetic testing in any individual study or in pooled analysis (male 98.4%; female 98.6%). In analyzing the rates of cumulative consent to genetic testing over time, 2 independent periods were identified when rates of consent were lower than anticipated, which coincided with times in which several studies were performed simultaneously (Fig. 3).

Table 1
Consent for genetic testing in clinical vaccine trials conducted at the Oxford Vaccine Group (see Supplementary Table 1 for study details).

Study	Total *n*	% Male	% Yes	Mean age all	Mean age Yes	Mean age No	Mean age mother Yes	Mean age mother No	Mean age father Yes	Mean age father No	Study reference
Infant study 1	136	47.4	94.9	0.15	0.17	0.15	32.2	32.0	–	–	Unpublished
Infant study 2	315	54.4	99.4	0.17	0.17	0.15	–	–	–	–	[31,32]
Infant study 3	19	49.5	89.5	0.15	0.15	0.15	–	–	–	–	Unpublished
Child study 1	230	58.0	95.2	9.1	9.1	9.2	40.8	39.7	43.4	45.1	[33]
Child study 2	169	51.6	91.1	3.0	3.0	3.1	–	–	–	–	[34]
Child study 3	276	51.4	98.2	4.3	4.3	2.7	–	–	–	–	[35]
Child study 4	64	55.2	100.0	3.4	3.4	–	–	–	–	–	Unpublished
Adolescent study 1	98	46.9	100.0	12.2	12.2	–	–	–	–	–	[36]
Adolescent study 2	1243	52.9	99.8	15.0	15.0	14.4	–	–	–	–	[32]
Adult study 1	150	44.0	100.0	50.8	50.8	–	–	–	–	–	Unpublished
Adult study 2	298	46.0	100.0	58.8	58.7	–	–	–	–	–	[37,38]
Total	2998	51.5	98.5								