ABSTRACT
Population-based research is enhanced by biological measures, but biological sampling raises complex ethical issues. The third British National Survey of Sexual Attitudes and Lifestyles (Natsal-3) will estimate the population prevalence of five sexually transmitted infections (STIs) (Chlamydia trachomatis, Neisseria gonorrhoeae, human papillomavirus (HPV), HIV and Mycoplasma genitalium) in a probability sample aged 16–44 years. The present work describes the development of an ethical approach to urine testing for STIs, including the process of reaching consensus on whether to return results. The following issues were considered: (1) testing for some STIs that are treatable and for which appropriate settings to obtain free testing and advice are widely available (Natsal-3 provides all respondents with STI and healthcare access information), (2) limits on test accuracy and timeliness imposed by survey conditions and sample type, (3) testing for some STIs with unknown clinical and public health implications, (4) how a uniform approach is easier to explain and understand, (5) practical difficulties in returning results and cost efficiency, such as enabling wider STI testing by not returning results. The agreed approach, to perform voluntary anonymous testing with specific consent for five STIs without returning results, was approved by stakeholders and a research ethics committee. Overall, this was acceptable to respondents in developmental piloting; 61% (68 of 111) of respondents agreed to provide a sample. The experiences reported here may inform the ethical decision making of researchers, research ethics committees and funders considering population-based biological sampling.

INTRODUCTION
Testing of biological samples in epidemiological research raises important ethical questions. The issues are particularly complex when applied to sexually transmitted infections (STIs) because of the stigma associated with diagnosis and the importance of confidentiality. Researchers are also faced with the decision of whether and when to disclose results to research participants. This paper describes the development of an ethical approach to urine-based STI testing in the third British National Survey of Sexual Attitudes and Lifestyles (Natsal-3).

Natsal-3 is a probability sample of 15,000 adults aged 16–74 years in Britain for which survey fieldwork started in 2010. It follows previous Natsal surveys in 1990 and 2000. The survey collects behavioural data, including sexual activity, partnership patterns, sexual function and health outcomes. In addition, Natsal-5 employs urine-based testing to estimate prevalence of Chlamydia trachomatis, Neisseria gonorrhoeae, human papillomavirus (HPV), HIV and Mycoplasma genitalium in a subgroup of 5000 respondents aged 16–44 years.

Benefits of biological testing in population-based research
Linking biological information to behavioural and demographic data can strengthen population-based research. For example, in 2000, Natsal-2 measured urinary C trachomatis prevalence, which informed the decision to extend national screening to men. Among many others, national surveys such as the UK Biobank, Health Survey for England (HSE), the English Longitudinal Study of Ageing (ELSA), the USA Health and Retirement Study (HRS) and the National Health and Nutrition and Examination Survey (NHANES) collect biological samples for biomarkers of disease. Biomarkers are not subject to reporting bias and lend considerable weight to the scientific reliability and precision of data, and may be used to validate self-reporting. These studies inform a wide range of health-related activities.

An ethical framework for biological testing in population-based research
Biological testing in population-based research also raises important ethical considerations, for which the bioethical principles (autonomy, beneficence, non-maleficence and justice), set out by Beauchamp and Childress, provide a framework. Beauchamp and Walters also identified four secondary principles: ‘fidelity’, ‘confidentiality’, ‘utility’ and ‘veracity’. The WHO and Joint United Nations Programme on HIV/AIDS (UNAIDS) applied these standards to guide the design of population-based surveys measuring HIV prevalence. First, respondents should ‘be protected from any harm’, which includes safeguarding respondent confidentiality. Second, respondents should ‘participate in the benefits of the research’. This is more complex because there may be no direct benefits for respondents in population-based surveys, but rather indirect societal benefits. Direct clinical benefits may occur where results are returned to respondents with advice and/or treatment. WHO/UNAIDS guidelines therefore suggest referral to free testing where results are not returned. Third, respondents should ‘be informed
of the procedures and risks. And fourth, respondents should ‘freely choose whether or not to participate in the study’.

International guidelines for HIV testing have distinguished between unlinked anonymous testing (UA), where results are irreversibly unlinked from the person tested, and linked testing, where results may or may not be returned. A programme of UA HIV surveillance testing has been successfully in place in the UK since 1990. However, the UA surveys differ from Natsal-3 in two key respects; (1) the UA research programme is not the primary reason for obtaining the sample tested, which is a routine sample and would otherwise have been discarded, and (2) individual consent for HIV testing on the leftover blood samples is not usually required.

Whether to return STI results in Natsal-3

Focus group studies suggest significant public interest in individual results from genetic research studies, but no studies have directly investigated preferences for obtaining results in the context of population-based STI research.

In designing Natsal-3, the decision to return STI results or not was an ethical concern because harm to respondents and their sexual partners might be avoided by returning results for treatable infections. Full disclosure is also consistent with upholding respect for respondents, and includes those wishing to participate only where results are returned. We considered the risks associated with not returning STI results against the alternative risks if named testing was conducted and results were returned.

METHODS

We undertook an extensive development phase to agree and test the acceptability and feasibility of STI testing in Natsal-3. The ethical principles described above informed our initial approach during the study funding process, and this was endorsed via independent peer review. An informed consensus was then sought through consultation with stakeholders including the Health Protection Agency (HPA), clinicians and the study’s Advisory Group (which includes representatives from the Terrence Higgins Trust, Family Planning Association and UK Department of Health). The approach was submitted to a NHS research ethics committee (REC) before piloting of the whole survey was undertaken in 23 postcode sectors across Great Britain. Within each sector, 25 addresses were randomly selected to yield a total sample of 575 addresses, of which 434 were residential with English-speaking and eligible occupants (aged 16–74 years). Interviews took place between March and May 2010. The response rate was 50.2%: 111 respondents aged 16–44 years reporting at least one sexual partner were invited to provide a urine sample.

RESULTS

The availability of free STI tests in Britain

For some STIs, there are specific recommended treatments with direct clinical benefits (table 1). However, it was argued that specific written details describing access to and availability of STI/HIV testing, as well as general sexual health information could be provided to respondents, and that these services provide a more appropriate setting for free diagnostic testing than is possible for Natsal-3. For C. trachomatis, there is now widespread testing in the community, and for young people since 2003, a national screening programme, such that an estimated 22.1% of 15–24 year olds were screened in 2010. Sexual health screening was less accessible in 2000, when Natsal-2 did return C. trachomatis results.

Accuracy and timeliness of survey tests

As in other surveys, the tests used in Natsal-3 may not reach the required level of clinical diagnostic accuracy, while still being sufficiently accurate for population prevalence estimates (table 1). Under study conditions some loss in sensitivity is expected, due to limitations on the specimen type and the need to transport, freeze and batch test samples, which may result in clinically unacceptable delays. The standard of diagnostic accuracy is a concern for all respondents. For example, a null or negative result feedback might result in undue reassurance and be without the health education messages that can be delivered when this occurs in a clinical setting. Providing STI test results, where the prevalence and therefore positive predictive values may be low raises the possibility of false positives, which would also cause harm through undue concern (table 1).

Results with unknown clinical and public health implications

For HPV and M. genitalium, the clinical and public health implications currently remain uncertain, such that a positive result may not require specific management, treatment or partner notification and may cause unnecessary and unethical distress (table 1).

A consistent approach supports effective communication

Providing results for some STIs, but not others, may be misinterpreted in that respondents may wrongly assume the results to apply to all STIs. A thorough understanding of the study design is a prerequisite for obtaining informed consent from respondents, and we argued that a uniform approach to test
results is easier to communicate, both for interviewers to explain and for respondents to understand.

**Practical considerations and cost efficiency**

In Natsal-2, where *C. trachomatis* prevalence was approximately 2%, a research nurse was employed to actively follow-up cases. Even with considerable effort, it proved impossible to contact 11% of cases with their results, and clinical outcomes were only available in half of contacted cases. Other authors have acknowledged the human and financial cost associated with appropriate return of results. For Natsal-3, non-return was argued to enable testing of a wider range of infections to identify coinfecion and associated risk factors. We reasoned that maximising the scientific output from biological testing is desirable, provided ethical principles are not compromised, and is consistent with an obligation to spend public research funds wisely.

**Acceptability**

In piloting, 61% (68 of 111) of respondents agreed to provide a urine sample without receiving results. In Natsal-2, in 2000, when *C. trachomatis* results were given, 71% of participants agreed. Few respondents raised concerns that results would not be returned. Some respondents were reassured after discussing their concerns with the interviewer. Data from the developmental phase were used to inform the study design and the patient information literature, and to support subsequent REC applications.

**DISCUSSION**

This paper describes the development of, and basis for, an ethically sound approach to STI testing within a large, population-based survey. Our approach was guided by ethical, practical and scientific principles and considerations. The testing of STIs and the decision not to return results was accepted by a REC, within the context that respondents were informed about and consented to this methodology. Although there are not direct benefits to participation, voluntary anonymised testing, with specific consent for this, including the knowledge that results will not be returned, was acceptable to respondents when piloted in Natsal-3.

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**Competing interests**

None.

**Patient consent**

Study subjects were members of the public rather than patients, and a specific consent form, approved by the research ethics committee, was developed for the study.

**Ethics approval**

Oxford A MREC.

**Contributors**

AMJ, as Principal Investigator for Natsal-3, and PS, Natsal-3 Co-Applicant, are joint senior authors with overall responsibility for this work. NF drafted this paper in discussion with all authors. All authors participated in its structure, content and preparation.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Data sharing statement**

The data presented in this study are pilot data, which are only accessible by the Natsal-3 study team. However, Natsal-3 survey data will be made publicly available after the end of the study through the UK data archive hosted by Essex University (http://www.data-archive.ac.uk).

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Testing for sexually transmitted infections in a population-based sexual health survey: development of an acceptable ethical approach

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