# Informed consent for research during epidemics and research integrity: challenges, controversies and lessons for the future

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# Summary

- Background to informed consent
- Unique features in an epidemic setting for research
- Challenges to the informed consent
- Alternate approaches to the informed consent
- Advantages and disadvantages
- Conclusion

# What is informed consent?

- A prerequisite to study participation
- Informed consent is a process
- Participant is given information they need to make a decision about participation in a study
- Ethics principle of respect for persons
  - Nuremberg code
  - Helsinki Declaration
  - Belmont report

# Considerations for informed consent

- Information
- Comprehension
- Voluntariness

*Belmont Report*

# Traditional informed consent

- Informed consent document
- Usually evidenced by a signed consent document
- Witness required

# Why research during an epidemic?

- Epidemics are events of nature
  - Natural setting/laboratory for an investigation/experiment
- Organism may be new or strain of existing organism may change
  - Genotyping and sero-epidemiology
- Describe the natural history
- Test new diagnostics, vaccines and treatments
- Postmortem research may further understanding of disease pathology

# Unique features during an epidemic

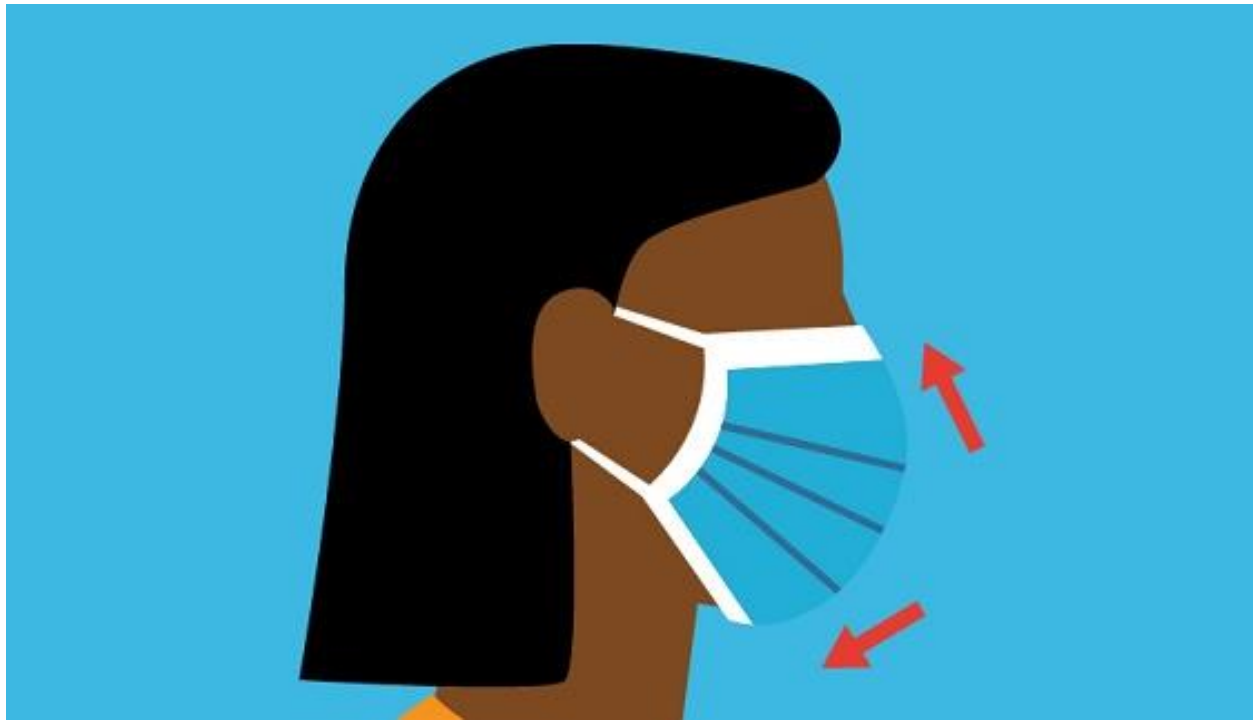
- Absence of standard treatment or standard of care
- High infection rates and or mortality
- Limited resources
- Tensions about priority of care versus research
- Infodemic
- Misconceptions about the disease
- Heightened levels of anxiety

# Challenges to the informed consent

- Study participants may be infectious
- Isolation or quarantined
- Lockdown or restricted movement
- Therapeutic misconception confounds understanding
- Information about condition is rapidly changing
- Admitted in the intensive care unit
- Voluntariness and decisional capacity
- Consent for research after death
- Bio-banking and risk of bio-piracy

# Study participants may be infectious

- Highly infectious agent
- High risk of transmission
- High basic reproductive rate
- Lack of sufficient PPE



# Isolation or quarantined

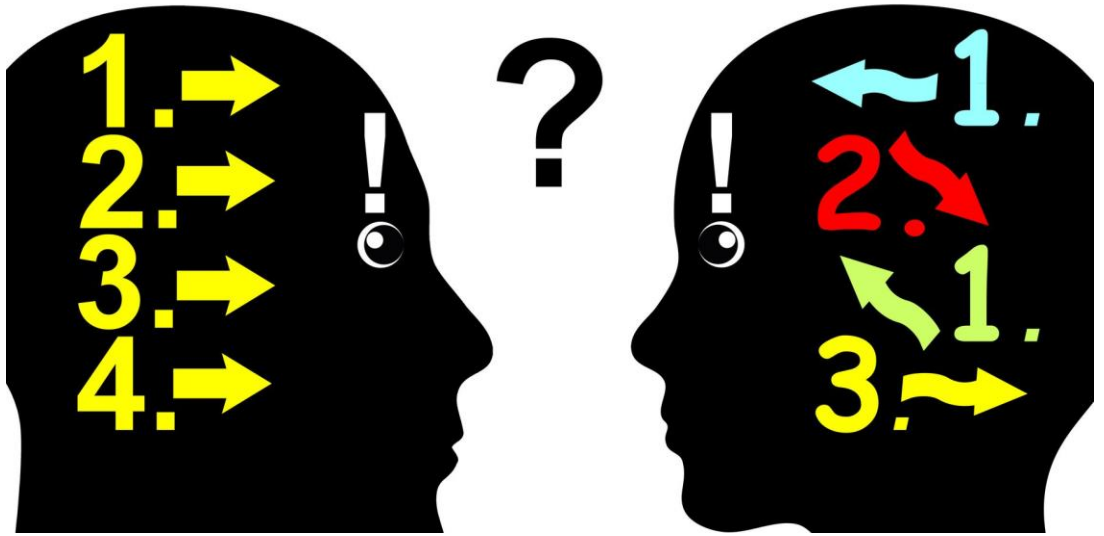
- Restricted access to potential study participants
- Mental health status due to isolation and social distancing
- Study participation is opportunity to “socialize”

# Lockdown or restricted movement

- Should research be considered an “essential” service?
- Public health interventions may conflict with proposed research activities

# Therapeutic misconception confounds understanding

- Is this research or treatment
- Absence of effective treatment
- Opportunity to access experimental products
- Randomization and placebo design?
- Inability to weigh the benefits versus risks



# Information about condition is rapidly changing


- Is the disease airborne, droplet transmission or not?
- Should I wear one mask or two?
- Does hydroxychloroquine work or not?
- Should I participate in a trial using Ivermectin?
- Should participants be ***re-consented*** when there is a shift in knowledge?

# Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka, Amit N Patel

## Summary

**Background** Hydroxychloroquine or chloroquine, often in combination with a second-generation macrolide, are being widely used for treatment of COVID-19, despite no conclusive evidence of their benefit. Although generally safe when used for approved indications such as autoimmune disease or malaria, the safety and benefit of these treatment regimens are poorly evaluated in COVID-19.

**Methods** We did a multinational registry analysis of the use of hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19. The registry comprised data from 671 hospitals in six continents. We included patients hospitalised between Dec 20, 2019, and April 14, 2020, with a positive laboratory result for SARS-CoV-2. Patients who received one of the treatments of interest within 48 h of diagnosis were included in one of four treatment groups (chloroquine alone, chloroquine with a macrolide, hydroxychloroquine alone, or hydroxychloroquine with a macrolide), and patients who received none of these treatments formed the control group. Patients for whom one of the treatments of interest was initiated more than 48 h after diagnosis or while they were on mechanical ventilation, as well as patients who received remdesivir, were excluded. The main outcomes of interest were in-hospital mortality and the occurrence of de-novo ventricular arrhythmias (sustained or non-sustained ventricular tachycardia or ventricular fibrillation).

**Findings** 96 032 patients (mean age 53·8 years, 46·3% women) with COVID-19 were hospitalised during the study period and met the inclusion criteria. Of these, 14 888 patients were in the treatment groups (1868 received chloroquine, 3783 received chloroquine with a macrolide, 3016 received hydroxychloroquine, and 6221 received hydroxychloroquine with a macrolide) and 81 144 patients were in the control group. 10 698 (11·1%) patients died in hospital. After controlling for multiple confounders (including sex, race or ethnicity, body-mass index, underlying cardiovascular disease and its risk factors, diabetes, underlying lung disease, smoking, immunosuppressed condition, and baseline disease severity), when compared with mortality in the control group (9·3%), hydroxychloroquine (18·0%; hazard ratio 1·335, 95% CI 1·2[illegible]457), hydroxychloroquine with a macrolide (23·8%; 1·447, 1·368–1·531), chloroquine (16·4%; 1·365, 1·218–1·531), and chloroquine with a macrolide (22·2%; 1·368, 1·273–1·469) were each independently associated with an increased risk of in-hospital mortality. Compared with the control group (0·3%), hydroxychloroquine (0·[illegible]; 2·369, 1·935–2·900), hydroxychloroquine with a macrolide (8·1%; 5·106, 4·106–5·983), chloroquine (4·3%; [illegible], 3·970–4·596), and chloroquine with a macrolide (6·5%; 4·011, 3·344–4·812) were independently associated with an increased risk of de-novo ventricular arrhythmia during hospitalisation.

**Interpretation** We were unable to confirm a benefit of hydroxychloroquine or chloroquine, when used alone or with a macrolide, on in-hospital outcomes for COVID-19. Each of these drug regimens was associated with decreased in-hospital mortality and increased frequency of ventricular arrhythmias when used for treatment of COVID-19.

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# Admitted in the intensive care unit

- What is the survival of participants admitted in the ICU?
- Are study participants able to consent?
- Next of kin may not be allowed to health facility
  - Too distressed or anxious to provide proxy consent

# Voluntariness and decisional capacity

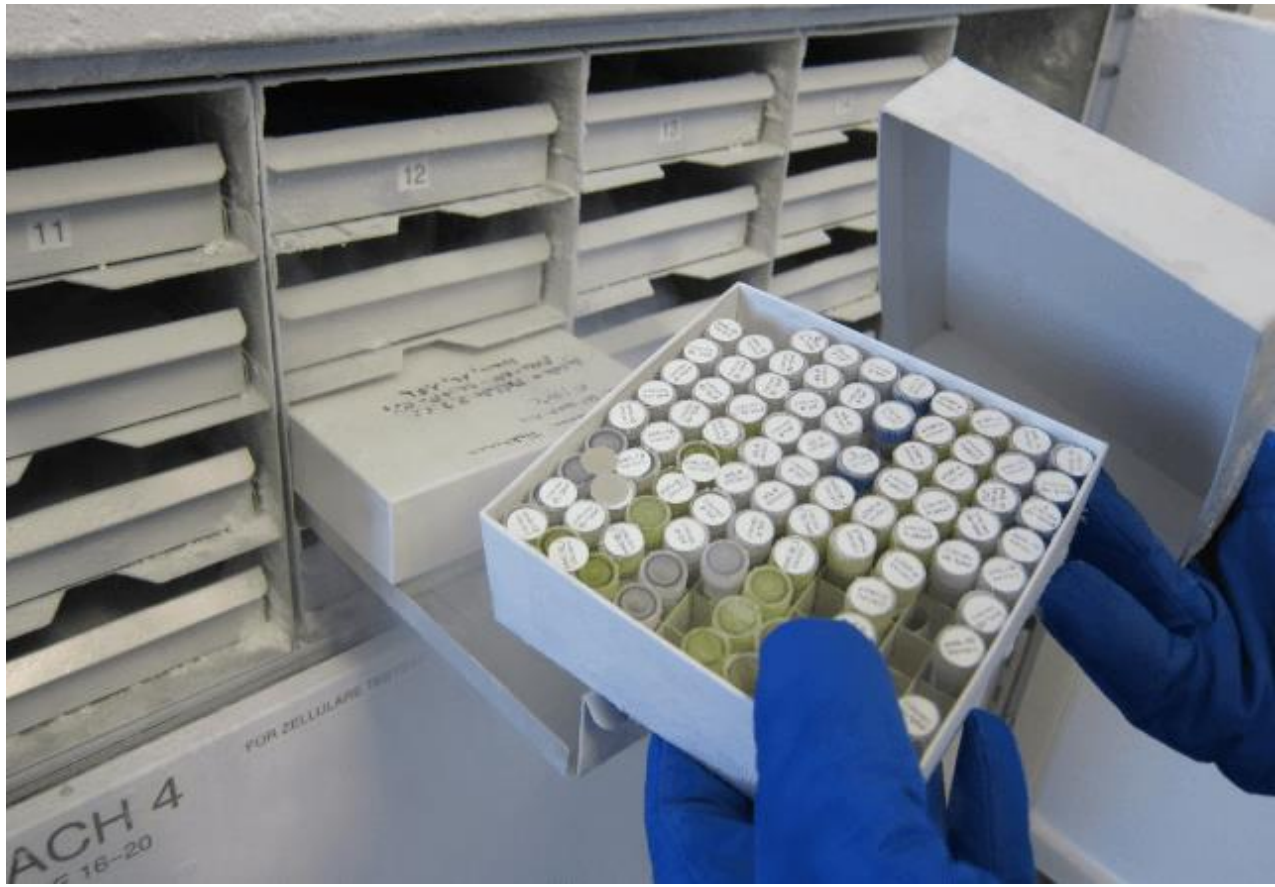
- Fear of infection or death
- Uncertainty
- Diminished capacity
- Vulnerability
- Should investigators measure voluntariness before consent participants?

# Consent for research after death

- Epidemics often cause significant mortality
- Valuable information may be held in clinical data and specimens
- Should data from dead participants be used?
- Who will consent for their use?
- Advance written notice

# Bio-banking and risk of bio-piracy

- Routine sample collection
  - Repurposing for research
- Storage of specimens
- Shipment of samples
- Data sharing
- Who consents for sharing?
  - Blanket or broad?
- Risk of biopiracy from the Ebola experience in West Africa



# Should research regulation be relaxed in an epidemic?

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- So, which regulations should be revised?
- And to what extent?

# Informed consent waiver

- Should informed consent be waived for research involving epidemics?

# Waiver of informed consent under 45 Code of Federal Regulations (CFR) 46.116 (d)

- The research involves no more than minimal risk to the subjects;
- The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- The research could not practicably be carried out without the waiver or alteration and
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

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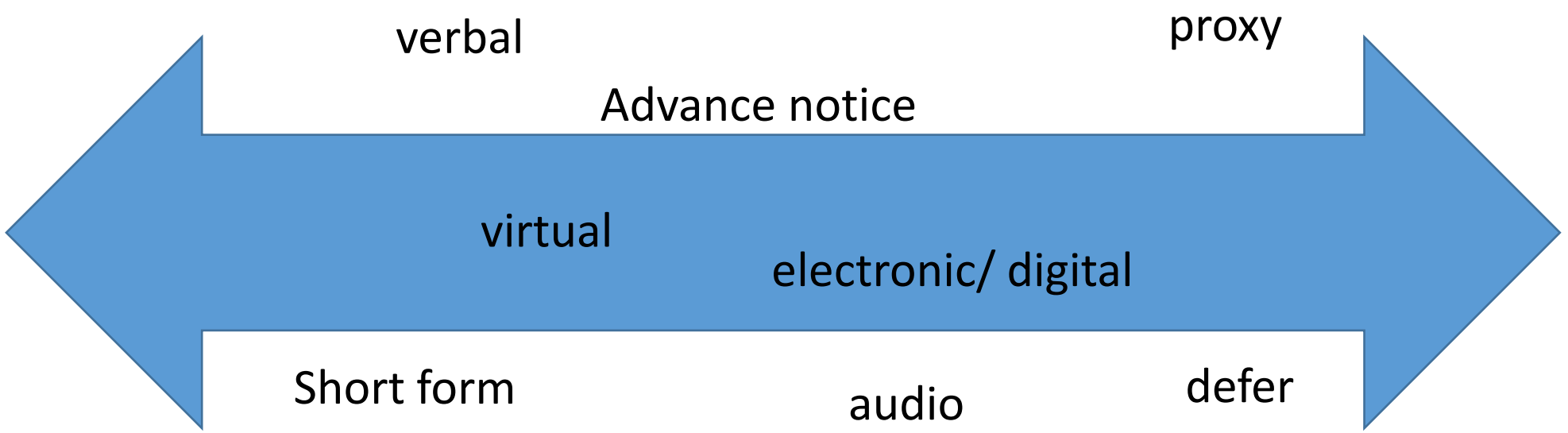
# Alternate approaches to informed consent process

- Verbal consent
- Short form consent
- Virtual consent
- Digital/ electronic consent (eConsent)
  - Electronic video
  - Video assisted informed consent
  - Audio
  - REDCap
- Advance notice
- Consent waiver followed by deferred proxy consent


verbal
proxy
Advance notice
virtual
electronic/ digital
Short form consent
audio
defer
Standard written informed consent
Waiver of consent

# eConsent

- COVID-19 has seen growth in the eConsent studies
- July 2020
- FDA released documents recommending eConsent over traditional consent, when appropriate technology is available

Original Paper

# Electronic Video Consent to Power Precision Research: A Pilot Cohort Study

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RESEARCH LETTER

# The Use of Electronic Consent for COVID-19 Clinical Trials: Lessons for Emergency Care Research During a Pandemic and Beyond

Eric Jaton[1], Jamie Stang[2], Michelle Biros, MD[1], Abbey Staugaitis, MSN[1], Julie Scherber[1], Florian Merkle, MD[1,2], Nicholas M. Mohr, MD, MS[3], Christopher Streib, MD, MS[4], Lauren Klein, MD, MS[1,2], and Michael A. Puskarich, MD, MS[1,2]

The novel SARS-CoV-2 coronavirus poses many unique challenges to the implementation of clinical research, particularly as it relates to the processes of informed consent. Traditional methods of in-person informed consent were no longer plausible, because face-to-face discussions may expose researchers and patients to increased risk of contracting and spreading the virus. In many circumstances the research personnel obtaining consent were consid-

The two main goals of eConsent are the same as traditional informed consent: first, to conduct a comprehensive discussion with the patient regarding study procedures so that they can make an informed decision about participation with a full understanding of the risks and benefits involved and, second, to document this conversation appropriately.[1] With eConsent, both of these goals can be achieved using a secure digital platform on an electronic device, eliminating the

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journals.sagepub.com/home/jre
SAGE

# Communicating With Diverse Patients About Participating in a Biobank: A Randomized Multisite Study Comparing Electronic and Face-to-Face Informed Consent Processes

**Christian M. Simon[1], Kai Wang[2], Laura A. Shinkunas[2], Daniel T. Stein[3], Paul Meissner[3], Maureen Smith[4], Rebecca Pentz[5], and David W. Klein[2]**

## Abstract

Some individuals' understanding of informed consent (IC) information may improve with electronic delivery, but others may benefit from face-to-face (F2F). This randomized, multisite study explores how individuals from diverse backgrounds understand electronic IC documents versus F2F, their confidence in understanding, and enrollment in research. A total of 501 patients at two U.S. biobanks with diverse populations participated. There were no overall differences between electronic and F2F understanding, but F2F predicted higher confidence in understanding and enrollment. Ethnicity and a higher educational level predicted higher understanding and confidence. Study findings suggest that electronic consent may lead to better understanding for non-Hispanic patients of higher socioeconomic status. F2F processes may lead to better under-

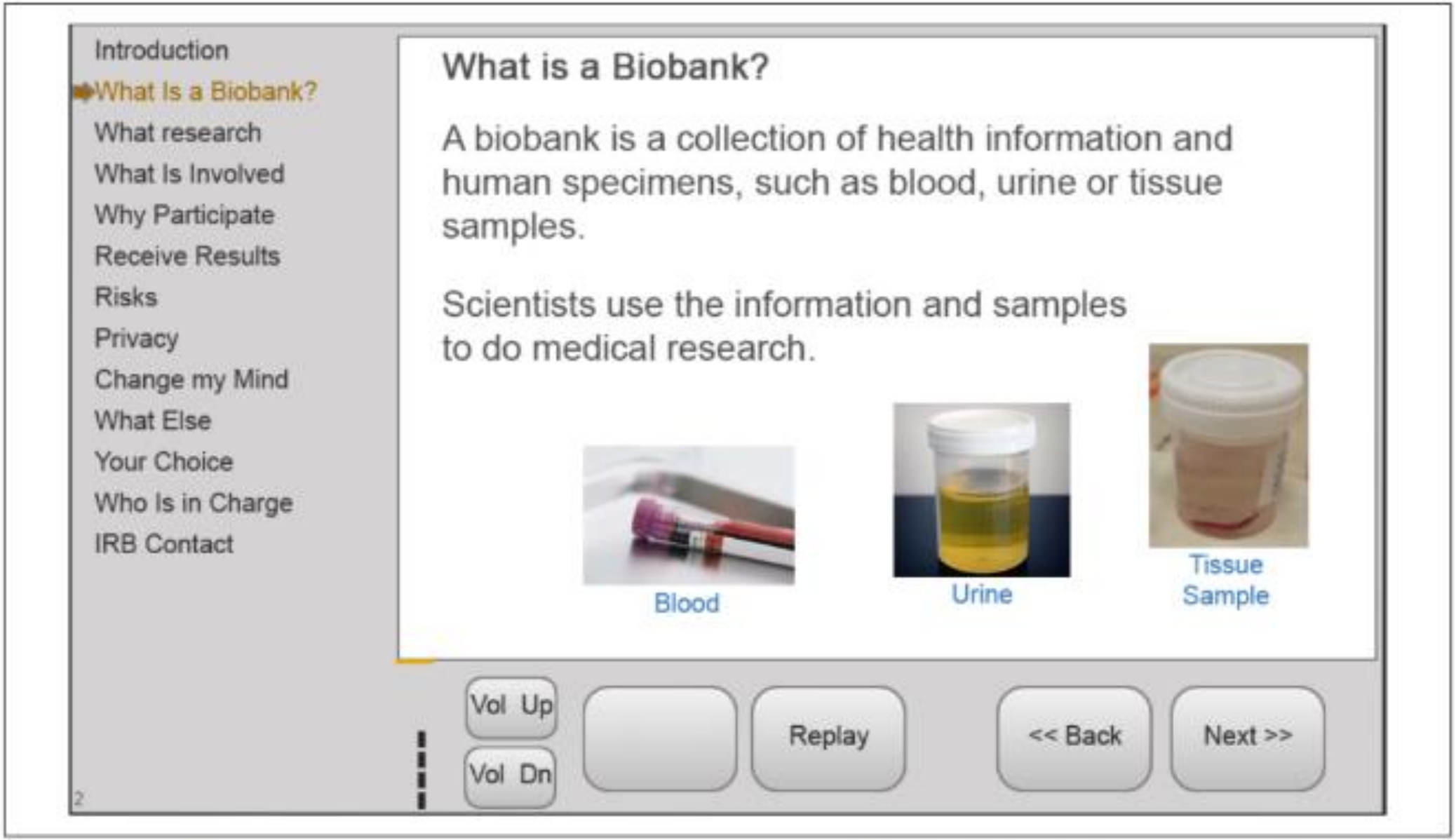


**Figure 2.** Sample electronic informed consent (eIC) screen using exact wording from the biobank consent document with added graphics.

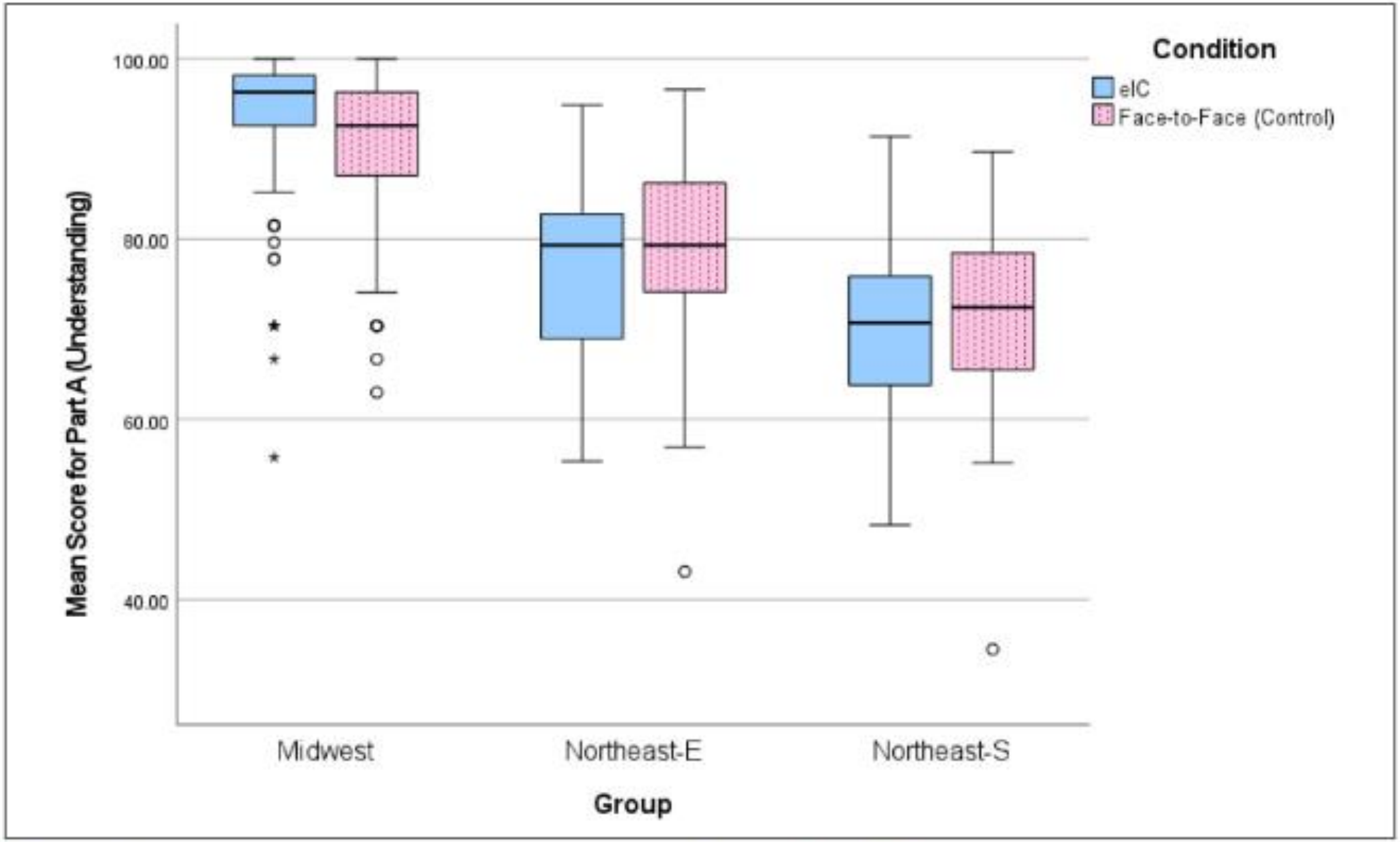


**Figure 3.** Box plot comparison of mean understanding scores for the group by condition (electronic informed consent [eIC] vs. face-to-face [F2F]).

BMJ Open

# Does electronic consent improve the logistics and uptake of HPV vaccination in adolescent girls? A mixed-methods theory informed evaluation of a pilot intervention

Tracey Chantler ,[1] Ellen Pringle,[2] Sadie Bell,[1] Rosie Cooper,[3] Emily Edmundson,[4] Heidi Nielsen,[4] Sheila Roberts,[4] Michael Edelstein ,[2] Sandra Mounier-Jack[1]

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► Prepublication history and additional material for this paper is available online. To view these files, please visit the journal

## ABSTRACT

**Objectives** To evaluate the usability and acceptability of an electronic consent pilot intervention for school-based immunisations and assess its impact on consent form returns and human papilloma virus (HPV) vaccine uptake.

**Design** Mixed-methods theory-informed study applying qualitative methods to examine the usability and acceptability of the intervention and quantitative methods to assess its impact.

**Setting and participants** The intervention was piloted in 14 secondary schools in seven London boroughs in 2018. Intervention schools were matched with schools using paper consent based on the proportion of students

## Strengths and limitations of this study

- The use of a theory-informed mixed-methods study design allowed us to measure the effect of a pilot e-consent intervention on immunisation performance and identify mechanisms that facilitated or impeded implementation.
- The study design allowed us to account for schools, nurses, data managers, parents and adolescents' experiences of using the e-consent technology in this evaluation.
- Data limitations include the lack of interviews with school staff to complement the feedback forms and

# Key considerations for e-Consent

- Accessibility and user-friendliness of e-consent
- User engagement and comprehension
- Customisability to participant preferences and demographics
- Data security –secure platforms
- Impact on research teams
- Integrity- guidance and compliance

Skelton E, Drey N *et al* 2020

# eConsent

## Benefits

- Infection control
- Enhanced understanding
- Remote enrollment
- Regulatory compliance- digital records
- Mitigate potential for in-person coercion

## Challenges

- Access to smart devices
- Illiterate to technology
- Assessing capacity
- Institutional policies

Jaton E, Stang J et al 2021

# Conclusion

- Informed consent remains a core component of ethical research including epidemic settings
- We should not seek for ways to circumnavigate the process
- Flexibility to adopt alternative, innovative and acceptable ways of obtaining informed consent
- Embrace the opportunities of technological advancement
- Collective effort of investigators, research ethics committees and regulatory bodies

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