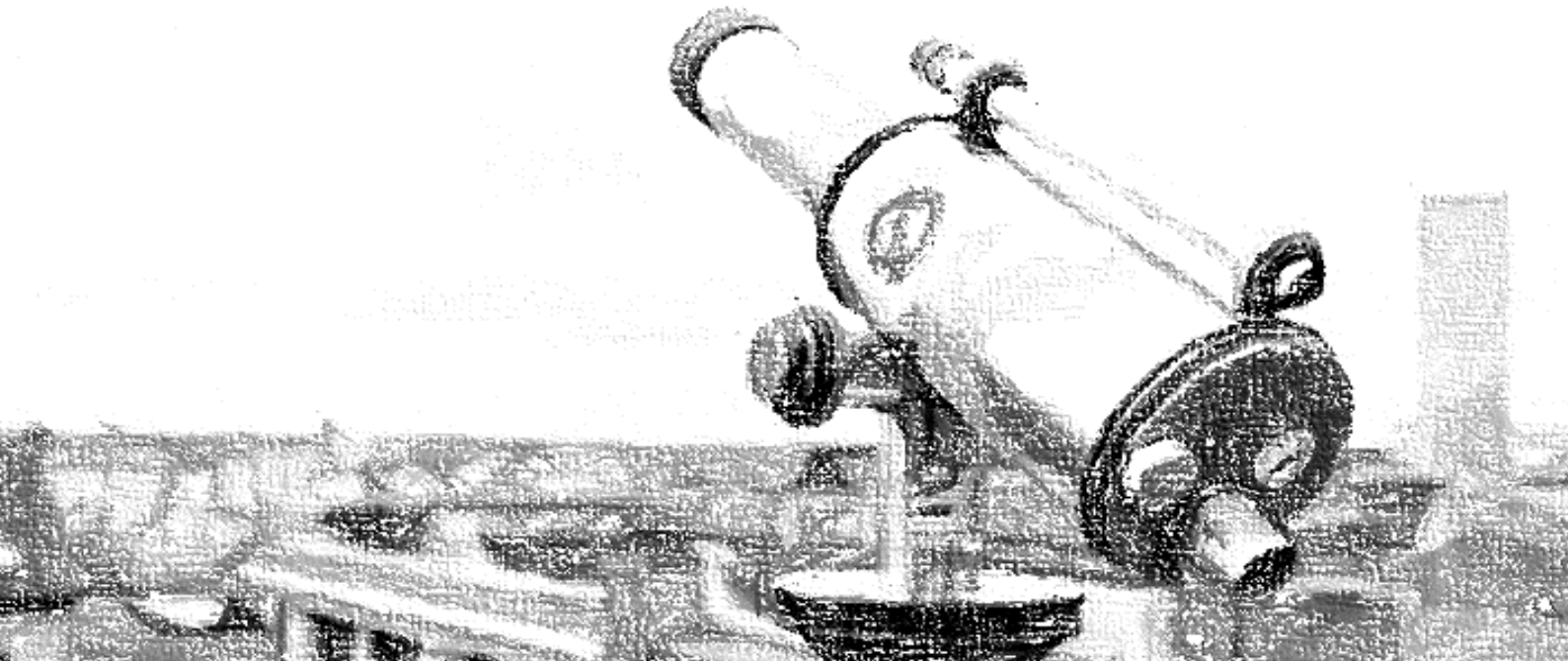
WORKSHOP REPORT

Rethinking informed consent: Emerging challenges in the digital era

26 March 2020



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About this publication

This report provides an overview of the online workshop "*Rethinking informed consent: emerging challenges in the digital era*", held on 26 March 2020. The workshop was organised by AND Consulting Group (AND-CG) as part of the i-CONSENT project (GA: 741856).

For more information about the i-CONSENT project, please visit www.i-consentproject.eu or email us at *info[at]and-cg.com*.

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Executive summary

On the 26th March 2020 AND Consulting Group (AND-CG) held an online workshop on challenges to informed consent processes in clinical trials in the digital era. This event was part of the EU-funded research project 'i-CONSENT' (full title: *Improving the guidelines for informed consent, including vulnerable populations, under a gender perspective*).[1]

The workshop aims were:

- To present an AND-CG report on ethics, privacy, and data protection issues arising from the use of ICT tools in the informed consent (IC) process in clinical trials.[2]
- To promote consensus on important issues impacting IC in the digital era.
- To anticipate potential policy initiatives to promote ethical use of ICT in the IC process in clinical trials.

Digitalisation, big data, and the re-use of health data make it difficult to adequately inform participants about the range of uses to which their data may later be put. Left unaddressed, such difficulties could undermine the validity of a participant's consent. The i-CONSENT project has investigated possible uses of ICT and other innovations to improve the delivery of key information to potential trial participants. As part of the i-CONSENT project, AND-CG produced a report addressing ethics, privacy, and data protection risks associated with these initiatives. In this workshop, four invited experts gave presentations on the impact of technology and digitalisation on IC processes in clinical trials:

- **Søren Holm**, Professor of Bioethics at the University of Manchester and Professor of Medical Ethics (part-time) at the University of Oslo
- **Marcello Ienca**, Senior Research Fellow at the Department of Health Sciences and Technology at ETH Zurich
- **Laurence Lwoff**, Head of Bioethics Unit and Secretary of the Committee on Bioethics at the Council of Europe
- **Magali Feys**, privacy and data protection lawyer at AContrario Law

In the first presentation of Session 1 ('*Perspectives on the future of consent in clinical research*') Søren Holm argued that with the increasing digitalisation of clinical research, participants should be able to manage their consent preferences over time as new information arises or the research develops. The presentation focused on approaches such as *dynamic consent*, *broad consent*, and *meta-consent*. In the second presentation, Marcello Ienca focused on the implications of big data and artificial intelligence (AI) on the IC process. These technologies have a lot to offer in the domain of clinical research, contributing to improvements in prevention, early detection, and explanation of diseases. However, IC practices were not developed with these technologies in mind, and serious challenges have emerged. Explaining relevant processes (e.g. algorithmic decision making), the potential for secondary use of

[1] The i-CONSENT consortium comprises 7 partners (including academia, research centres, industry, patient organisations and SMEs) from 4 countries. The project is funded by the European Union under grant no. 741856. See www.i-consentproject.eu for more details.

[2] A summary of this report is provided in Annex 4 below. For the full report, please contact AND-CG (info[at]and-cg.com).

data, and associated risks (which differ from 'traditional' health or safety risks) to participants is no simple matter. Ienca presented strategies to address these challenges, including ensuring inclusiveness in the IC process, innovating consent models for big data research, and promoting transparency about technology.

Discussion in this session also addressed emergency clinical trials taking place to combat the ongoing COVID-19 pandemic. Several risks to privacy and fundamental rights were highlighted, though no specific mitigation measures were recommended. It was recalled that derogations from fundamental rights and data protection standards are allowed for matters of public health. These should be subject to strict time and purpose limitations.

Session 2 ('*The European regulatory landscape for consent in clinical research*') focused on the regulatory framework governing the role of IC in the digital era. Laurence Lwoff gave the first presentation. She provided an overview of the legal framework adopted by the Council of Europe (CoE) to govern IC in biomedical research, including for secondary uses of health-related data and biological samples. Lwoff's presentation gave insight into the recently adopted *Strategic Action Plan on Human Rights and Technologies in Biomedicine 2020-2025* (SAP). This addresses ethical and fundamental rights challenges presented by technology in biomedicine and biomedical research, including those that relate to the IC process. In the second presentation of Session 2, Magali Feys presented the data protection framework governing the role of consent to the processing of health-related data in clinical trials. The presentation especially focused on the recent *Opinion 3/19 issued by the European Data Protection Board (EDPB) concerning Questions and Answers on the interplay between the Clinical Trials Regulation (CTR) and the General Data Protection regulation (GDPR).* This Opinion had been observed to have serious implications for the IC process in clinical trials.

This workshop was an opportunity to exchange views on some of the most important challenges to IC in clinical trials in the digital era. Overall, the presentations and discussion suggested that, in the face of the digitalisation of clinical research, traditional approaches to IC are increasingly unable to adequately protect the interests of trial participants. IC processes must evolve and adapt to the new realities of biomedical research, but further research is required to develop innovative models of consent that protect the interests of 21st century research participants.

List of abbreviations

AI	Artificial Intelligence
AND-CG	AND Consulting Group
CoE	Council of Europe
CTR	Clinical Trials Regulation 2014
DH-BIO	Committee on Bioethics of the Council of Europe
EDPB	European Data Protection Board
EDPS	European Data Protection Supervisor
EU	European Union
FISABIO	The Foundation for the Promotion of Health and Biomedical Research of the Valencian Region
GDPR	General Data Protection Regulation 2016
IC	Informed consent
i-CONSENT	An EU-funded project (GA: 741856), full title: *Improving the guidelines for informed consent, including vulnerable populations, under a gender perspective*
ICT	Information and communication technology
IRB	Institutional Review Board
REC	Research Ethics Committee
SAP	Council of Europe *Strategic Action Plan on Human Rights and Technologies in Biomedicine 2020-2025*
WMA	World Medical Association

Introduction

This workshop was organised by AND Consulting Group (AND-CG) within the scope of the EU-funded research project i-CONSENT (full title: *Improving the guidelines for informed consent, including vulnerable populations, under a gender perspective*). It took place on the 26th March 2020 and focused on the impact of the digitalisation of clinical trials on the informed consent (IC) process. The workshop aims were:

- To present an AND-CG report on ethics, privacy, and data protection issues arising from the use of ICT tools in the IC process in clinical trials.[3]
- To promote consensus on important issues impacting IC in the digital era.
- To anticipate potential policy initiatives to promote ethical use of ICT in the IC process in clinical trials[4]

In the introductory session Dimitris Dimitriou, Director at AND-CG, welcomed the participants. Javier Díez-Domingo, Head of the Vaccine Research Department at FISABIO[5] and i-CONSENT Project Coordinator, gave an overview of the i-CONSENT project. Silvia Lorenzo-Perez presented findings from AND-CG's research into ethics, privacy, and data protection challenges in the use of ICT in the IC process in clinical trials (see also Annex 4).

Session 1 focused on the future of consent in clinical research. It included presentations by Søren Holm on innovative approaches to the IC process that are adaptive to participants' (possibly) changing consent preferences, and by Marcello Ienca on the implications of big data and AI on the IC process. Session 2 addressed the regulatory landscape governing consent in clinical research in Europe. The first presentation was given by Laurence Lwoff about the work carried out by the Council of Europe (CoE) to advance the role of IC and react to the challenges posed by new technologies in biomedical research. The second presentation, by Magali Feys, described recent developments in data protection law that impact consent practices for clinical trials. All presentations were followed by interactive sessions where participants could address questions to the speakers and exchange views on key topics.

The i-CONSENT project conceptualises IC as a five-stage process, beginning with a participant's first contact with a clinical study and continuing for the duration of their involvement in it. The five stages are presented in Figure 1.

[3] A summary of this report is provided in Annex 4 below. For the full report, please contact AND-CG (info[at]and-cg.com).

[4] Recognising the challenges posed by the digitalisation of healthcare and clinical research, European regulatory bodies have called for dialogue between relevant actors to identify risks and opportunities. As recently pointed out by the European Data Protection Supervisor (EDPS) and the Council of Europe's Committee on Bioethics, it is crucial that all stakeholders in clinical research, as well as experts in other relevant areas, engage in constructive dialogue to achieve a common understanding and develop recommendations to address the major challenges.

[5] The Foundation for the Promotion of Health and Biomedical Research of the Valencian Region.

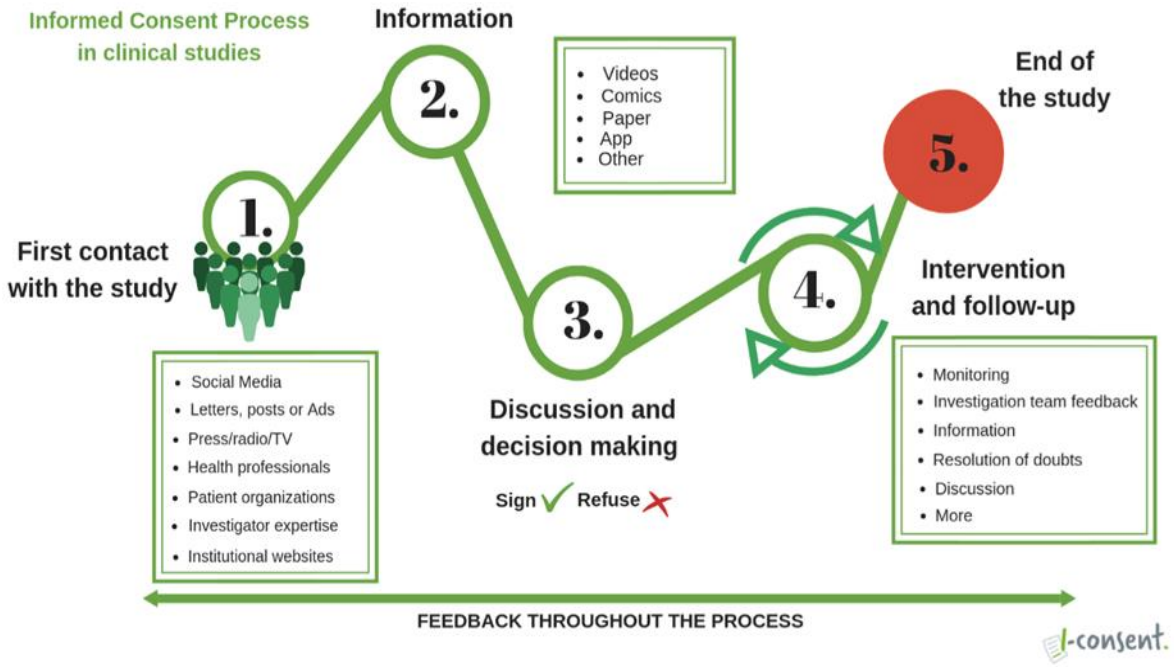

Figure 1- Schematic representation of the informed consent process

Whilst digitalisation and technology present issues across all stages of the IC process, the workshop mainly addressed the use of health-related data stored for future research purposes after the end of a clinical trial (i.e. 'secondary uses' of data). The rapid development of digitalisation and big data processing make it difficult to fully inform participants and data subjects of every secondary use of their data. Left unaddressed, such difficulties could undermine the validity of a participant's consent.

Overall, the workshop presentations and discussion suggested that, in the face of the digitalisation of clinical research, traditional approaches to IC are increasingly unable to adequately protect the interests of trial participants. IC processes must evolve and adapt to the new realities of biomedical research, but further research is required to develop innovative models of consent that protect the interests of 21st century research participants.

Welcome Session

Presenters	Title of presentation
Javier DÍEZ-DOMINGO	*Rethinking informed consent – the i-CONSENT project*
Silvia LORENZO-PEREZ	*Informed consent in the digital era*

J. Díez-Domingo: Rethinking informed consent – the i-CONSENT project

Javier Díez-Domingo is Head of the Vaccine Research Department at FISABIO and scientific coordinator of the i-CONSENT project. He explained that the aim of the i-CONSENT project is to address serious deficiencies associated with traditional approaches to IC by producing a set of guidelines to improve the IC process. Too often, the IC process in clinical trials is viewed merely as a means of documenting an agreement between the participant and the sponsor, rather than as a process through which prospective participants are given all the information they need to make an informed choice about participation. As a result, IC forms are often too long, written in complex technical language that a lay person finds difficult to understand, and unpleasant to read.

Díez-Domingo argued that the IC process should be updated to reflect societal realities. i-CONSENT's first step in this is an insistence that IC should no longer be treated as a one-off event, but as a process lasting the entire length of a participant's involvement in a study (see Figure 1). Information should be presented in clear and accessible formats, exploiting opportunities to use ICT and online approaches where appropriate. The i-CONSENT guidelines aim to improve IC processes by promoting effective information delivery, participant autonomy, respect for gender, cultural, ethnic or religious background, and responsible use of ICT and other innovative approaches.[6]

S. Lorenzo-Pérez: Informed consent in the digital era

In 2019, in the scope of the i-CONSENT project, AND-CG produced a report examining ethics, privacy, and data protection issues raised by the use of ICT in the IC process in clinical trials. Silvia Lorenzo-Pérez, Research Officer at AND-CG, presented selected highlights of this work. Descriptions of the technologies analysed and the ethical, privacy, and data protection issues identified can be found in the scene-setting report, which was provided to participants ahead of the workshop (see Annex IV), as well as in the full study report.[7]

The innovative approaches and technologies examined in the AND-CG report included:

- *Enhanced IC forms.* Non-technological steps such as making forms simpler and shorter, presenting information graphically, or using a 'tiered' approach.

[6] See the i-CONSENT project website for further details: www.i-consentproject.eu.
[7] The full report is available upon request: please contact AND-CG at info[at]and-cg.com.

- *Multimedia tools.* Approaches using video, audio, online resources, tablet or mobile apps, etc. to make information more accessible, enhance interactivity, decouple comprehension from education level, and enable assessment of comprehension.
- *Dynamic consent.* ICT platforms enabling real-time management of participants' consent preferences (e.g. consenting to participate in, or donate data to, new trials).
- *IC training for researchers / healthcare professionals.* Training in communicating complex information for IC processes understandably.

The following associated ethical issues were highlighted.

- *Importing existing problems of consent*. Consent can be problematic for online services. Users rarely read terms and conditions before consenting; and frequent requests to confirm consent lead to consent-fatigue and 'routinisation'.
- *Autonomy:* Online tools may accentuate distancing of participants from researchers. This may place too much responsibility on participants to be wholly responsible for coming to their decision (autonomy and independence are distinct).
- *Monitoring comprehension*. Technologies for monitoring or evaluating comprehension may be (or be perceived as) comparable to forms of online surveillance (which can undermine fundamental rights and civil liberties).
- *Personalisation and discussion*. Technology can enhance information disclosure, but it must be a support, rather than alternative, to face-to-face researcher-participant discussion (discussion is the most important part of the IC process).
- *Trust in the technology.* Technologies must be designed for inclusivity and transparency.
- *Broad consent vs. dynamic consent*. Broad consent may be incompatible with genuinely *informed* consent. Dynamic consent may extenuate consent fatigue, routinisation, and may not best serve societal interests in health research.
- *Quality of information*. It is impossible to guarantee participants will not be exposed to unreliable information on the Internet. Researchers must find effective ways to counter questionably sourced information.
- *Institutional Review Boards (IRBs) and Research Ethics Committees (RECs)*: IRBs and RECs have limited capacity to assess technologies proposed for IC processes. This may be a barrier to uptake of innovative tools and techniques.
- *IC and data protection.* The EDPB has proposed that personal data processing in clinical trials may require a legal basis under the GDPR other than consent. This adds complexity to the information that should be disclosed to participants.

Session 1: Perspectives on the future of consent in clinical research

Presenters	Title of presentation
Søren HOLM	*Consent solutions for secondary use of trial data after the end of the trial*
Marcello IENCA	*The implications of big data for informed consent*

S. Holm: Consent solutions for secondary use of trial data after the end of the trial

Søren Holm, Professor of Bioethics at the University of Manchester and Professor of Medical Ethics (part-time) at the University of Oslo, presented on the so-called 'secondary use problem' – of managing the further use of trial data in ways that respect participants' rights and wishes but also serve society's interest in health research – and approaches to IC that could address it. Three approaches were discussed: broad consent, dynamic consent and meta-consent.

Holm explained that, for biobanking, the standard approach has been *broad consent*. With broad consent, research subjects, at the point of donating biological material or data, also consent (or don't) to certain kinds of future research. He argued that broad consent fails to satisfactorily address secondary uses of data because, at the point of giving consent, participants tend to be focused on the potential benefits of participation in the *current* trial, rather than on the implications of future uses of their data or samples. In Holm's view, the validity of this consent is questionable as the participant may be motivated by reasons that do not bear on the proposed future use (but only or mainly on the present trial).

Holm further argued that broad consent is afflicted by an 'expiry problem': people consent to what they understand at a very specific point in time. This creates two problems:

1. Consent is referentially opaque: what the listener (i.e. participant) understands from the information received may be different to what the speaker (i.e. researcher) meant.
2. Over time it becomes more uncertain what the original consent meant.

Holm noted that the expiry problem can be 'solved' by making consent broader and more unspecific; but this eventually collapses broad consent into 'blanket consent' (i.e. consent to *any* future use of data), which is highly ethically questionable.

Holm then argued that dynamic consent platforms are suboptimal due to high implementation costs. He further argued that in projects where researchers need to exploit data from more than one trial, there is a risk of inconsistency between consent preferences from participants across the different trials. Finally, Holm argued that a dynamic consent approach is liable to overload participants with requests for consent. This is particularly so for patients with chronic conditions or people participating in multiple trials.

Holm put forward 'meta-consent' as a solution to the secondary use problem. On a meta-consent approach, data subjects are able to state, upfront, their consent preferences – what

kind of consent they wish to give – for research use of their health and non-health data (see Fig. 2). These preferences then govern when and how participants are asked to consent in the future. For example, someone could give blanket consent to secondary use of one type of data in non-commercial contexts, broad consent to secondary use of another type in another context, and so on.

Meta-Consent		Types of Consent (X)							
Types of Data (Y)		**Specific**		**Broad**		**Blanket**		**Refusal**	
EPR (Electronic Patient Record)									
Tissue / Genomic data									
Health databases									
Linkage to non-health data									
Types of Context (Z)		**Specific**		**Broad**		**Blanket**		**Refusal**	
Private	Public								
Commercial	Non-commercial								
National	International								

Figure 2 - Example of meta-consent structure

Holm described the demonstration of a meta-consent smartphone app in Denmark (See Fig. 3). Holm argued that meta-consent can address the challenges of secondary data use in countries that enjoy reasonably well-functioning administrative structures. This is based on the following reasons:

1. The solution is general – not linked to any specific research project or trial.
2. It carries low transaction costs for researchers.
3. Users can state and modify their consent preferences and tailor which consent requests they will get in the future.
4. It provides a flexible architecture for communicating consent requests and responses between potential participants and researchers.

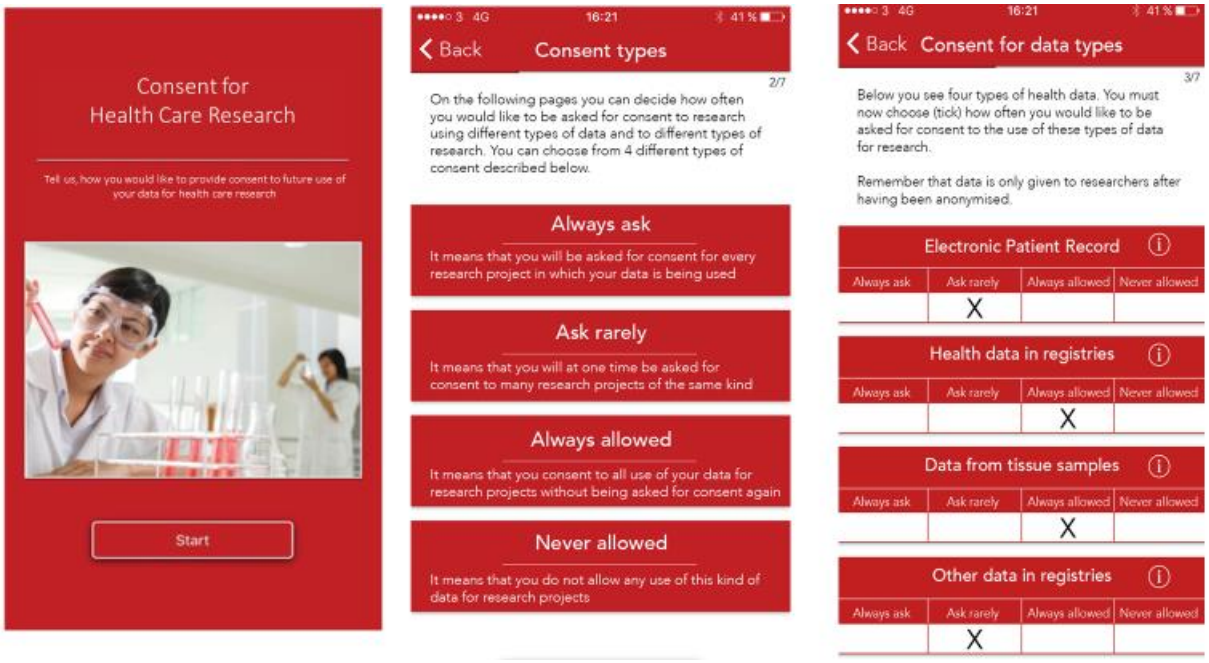

Figure 3 - Screenshots of meta-consent mobile app demonstration

Discussion

Question / Comment: Participants asked how the tool had been tested and whether factors such as age, culture, gender or geographic location influenced consent preferences.

Presenter response: The tool has been tested among a relatively small group in Denmark. As the objective of testing had been to assess the practicability of implementing the model via a mobile app, the volume of data collected did not allow for comparison of preferences among different populations. Holm suggested that, in Denmark, differences between first, second and third generations of immigrant communities and the native Danish community could be expected; but no such meaningful research has yet been carried out.

Question / Comment: Participants asked whether meta-consent could support responses to problems associated with cross-border data flows for emergencies such as COVID-19.

Presenter response: Holm noted that since access to Danish data is not currently restricted to Danish researchers, neither would it be so restricted if the meta-consent model were to be implemented. Implementation of meta-consent in Denmark would give people more control over their data than they have at present, because a lot of this research can currently take place without any form of consent. However, if it were implemented in Norway, where people now enjoy some control, it would make the process of consenting much more explicit. The implications in practice would depend on how existing EU legislation has been interpreted in individual countries.

Question / Comment: Participants asked whether the implementation of meta-consent would require review by RECs.

Presenter response: Holm clarified that meta-consent would be implemented at state (national) level, which would not require direct involvement of RECs. Denmark has very extensive and well-ordered health databases and regularly conducts research that links these data with other non-health data (e.g. employment records). The main purpose of implementing meta-consent in Denmark would be to give people control over the kind of research their data are used for.

Question / Comment: Participants asked whether there is foreseeable potential for meta-consent to be implemented in clinical trials.

Presenter response: Holm argued that meta-consent would be valid for all kinds of research on health-related data. In view of the latest developments concerning open science, he highlighted that ongoing trends indicate that it could become a requirement for sponsors and researchers to allow much more open access to clinical trial data, including for linkages with other data sets.

Question / Comment: A participant pointed out that a great deal of the personal data processing taking place in response to COVID-19 would not be possible in normal circumstances. A question was raised as to whether it could become more acceptable to adopt a broad consent model – or even to bypass consent altogether – in emergency situations.

Presenter response: Holm replied that in the UK, restrictions on the use of health-related data have been relaxed for COVID-19. Should it emerge that this data processing has been

crucial to the response, there is a real possibility of a shift towards a model where health data becomes much more accessible without consent.

M. Ienca: The implications of big data for informed consent

Marcello Ienca, Senior Research Fellow at the Department of Health Sciences and Technology at ETH Zurich gave a presentation on the implications of AI and big data for IC. Ienca clarified that while there is no consensus definition of 'health-related big data', we may describe it as 'extremely large datasets of heterogeneous data produced at high frequency that can be further processed computationally to reveal patterns, trends, and associations relating to human health' (Ienca et al. 2018, PLOS One). Ienca pointed out that big data processing increases the availability of 'real-world data', i.e. non-trial data that can be triangulated with data from clinical trials for healthcare decision-making. Real-world data, processed through big data analytics, can help improve prevention, early detection, explanation of diseases, and personalised medicine.

Ienca identified five ethical issues associated with AI and big data in clinical research and then discussed how these impact IC.

1. **Issue:** Big data analytics relies on continuous monitoring of compliance/adherence among research participants.
   Relevance to IC: IC was not developed to operate in the digital data ecosystem. Many bioethicists argue that traditional consent mechanisms are ill-suited to govern the collection of heterogenous data in an unsupervised manner, or the recycling of collected data (cf. Kahn et al., 2014).
2. **Issue:** AI and big data increase possibilities reidentifying research participants.
   Relevance to IC: There is no standard guidance on the communication of digital risks (which differ from risks that are typically communicated in the IC process).
3. **Issue:** AI and big data make possible the inferring of sensitive information from non-sensitive data.
   Relevance to IC: People may consent to the processing of non-sensitive data, unaware of the sensitivity of possible inferences.
4. **Issue:** Ubiquitous data points and sensor-equipped autonomous systems can generate and collect volumes of data without the knowledge or consent of subjects.
   Relevance to IC: Data may be collected without IC in a variety of ways. E.g. data subjects may be unaware of data harvesting from anonymised data sets or social media (arguably considered 'public-by-default').
5. **Issue:** AI can be used to profile people based on population-scale data.
   Relevance to IC: Many AI algorithms elude IC because no causal explanation can be given to data subjects about how algorithms produce a certain output (the 'black box problem' of AI, see Fig. 5 below). In clinical research settings, this may lead to algorithmic bias and algorithmic discrimination: e.g. algorithmic bias in skin cancer detection could have disproportionately negative consequences for certain ethnic groups.

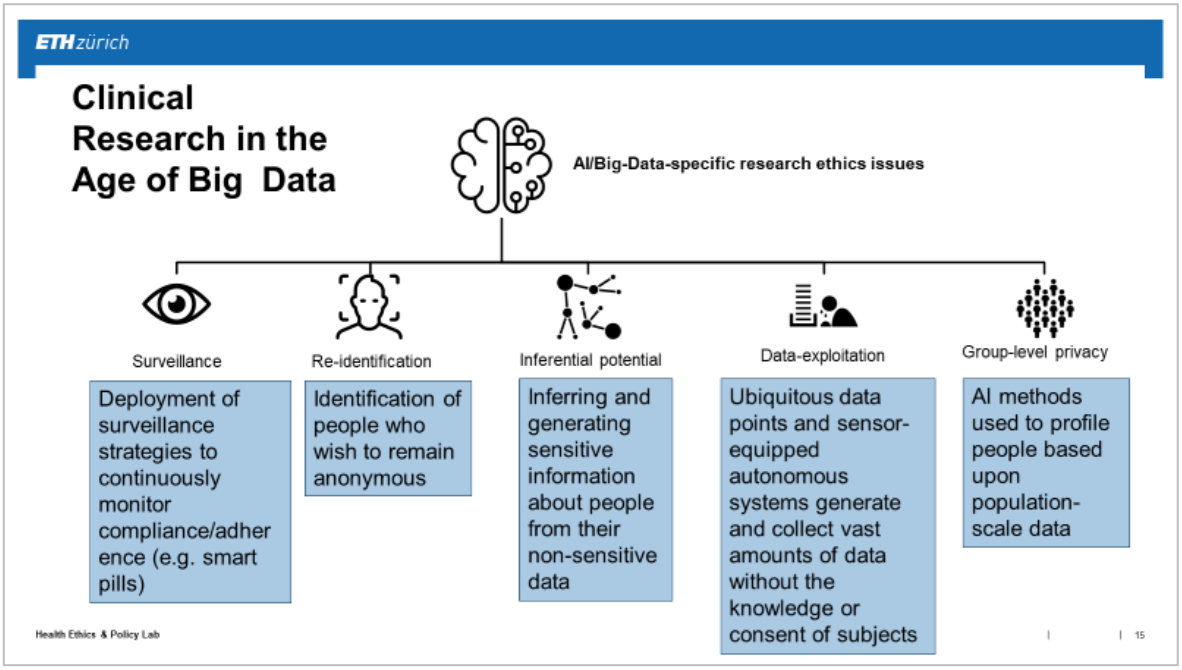

Figure 4 - AI & Big data - specific ethical issues

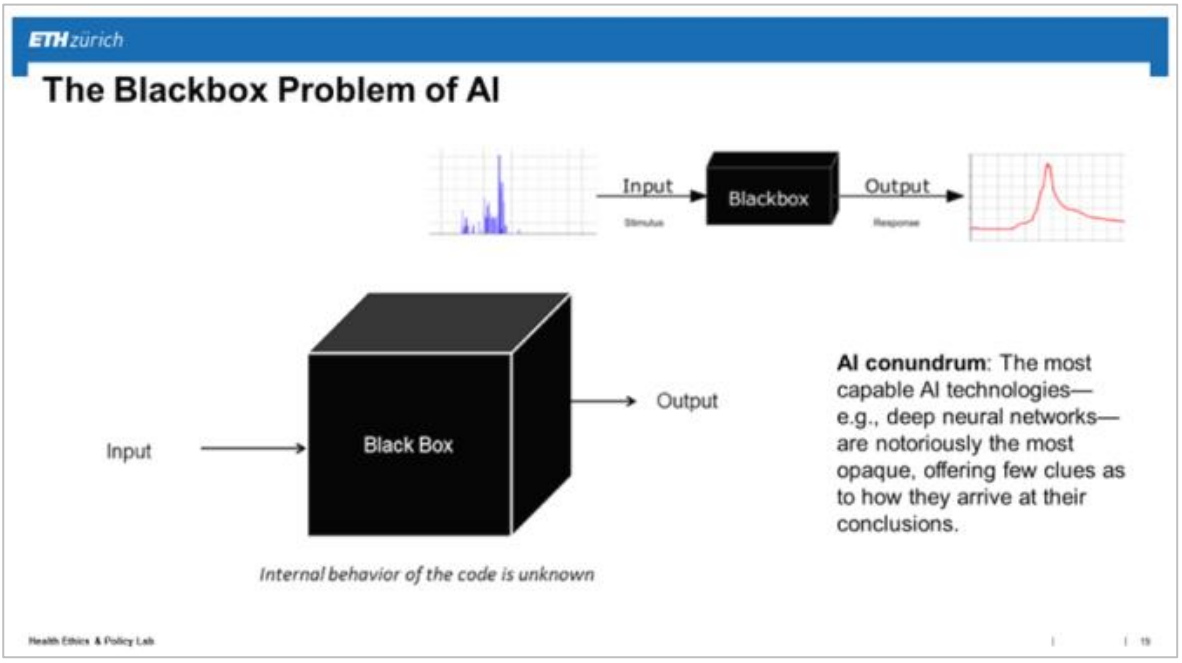

Figure 5 - Representation of the 'black box problem'

Ienca suggested the following strategies to address the abovementioned issues:

1. **Inclusiveness:** AI and big data research must promote 'inclusiveness' in relation to the IC process, so that coercion can be avoided and participants are given adequate information about safeguards to avoid bias and discrimination.
2. **Amplification:** The variety of consent models used in this type of research should be amplified or expanded to include adaptive and context-specific consent models (e.g. Portable Legal Consent or meta-consent). These adaptive consent models should also be used in the context of non-conventional health research.
3. **Transparency:** AI technologies should be explainable and transparent. Algorithms should be fair, auditable and susceptible to inspection. Participants should be adequately informed about (i) data protection measures; (ii) if/how data will be reused; (iii) when and for what purposes AI is being applied in analytics; (iv) the major sources of data; (v) methods used to train AI algorithms.

Discussion

Question / comment: Ienca was asked to give his perspective on the use of AI and big data processing in the COVID-19 response.

Presenter response: Ienca replied that contact tracing tools and surveillance strategies are predicated on lawful derogations from legal standards for reasons of public health. Emphasising the exceptionality of these measures, he pointed out that the public perception of health-threats potentially makes individuals more likely to trade-off their rights to combat them. Ienca noted that data protection authorities, including the EDPB, have been positive about temporarily suspending some stricter GDPR requirements, enabling processing of personal data without consent, provided certain minimal conditions are met (EDPB, 2020). Ienca notes other minimum safeguards requiring researchers to demonstrate that the analytical model they are using is suitable for the specific purpose, and that its use is justified by scientific evidence. In addition, Ienca highlighted that it may be necessary to demonstrate that no other less privacy-invasive analytical model was available.

Open discussion: Ienca's response sparked general discussion of related issues. The following key points arose.

- It was argued that research authorities and technology developers must understand that data collected in this period cannot be used for other purposes.
- Lwoff (speaker, Session 2) noted that IC requirements apply even in emergency situations, though the process may be 'streamlined', e.g. consent may not need to be explicit, as it would in ordinary situations.
- Feys (speaker, Session 2) noted that the GDPR framework allows the processing of health-related data for research without relying on exceptions as per Article 9 GDPR (which includes public health).
- Large technology companies can support investigating institutions in collection and processing of data, but they should not seek to profit from the current situation. Feys argued that there is a real risk that some non-European companies do not operate

within the GDPR requirements of anonymisation, transparency and purpose limitations. Ienca pointed out that some of these companies have been observed to enable back-door data uses without explicitly mentioning it at the point of data collection (e.g. sharing data with law enforcement authorities).

Session 2: The European regulatory landscape for consent in clinical research

Presenters	Title of presentation
Laurence LWOFF	*Informed consent – Council of Europe reference work and new challenges*
Magali FEYS	*Does the EDPB force us to come up with another legal ground under GDPR for clinical trials?*

L. Lwoff: Informed consent – Council of Europe reference work and new challenges

Laurence Lwoff, Head of Bioethics Unit (DGI – Human Rights Directorate) and Secretary of the Committee on Bioethics (DH-BIO) at the Council of Europe (CoE), provided an overview of CoE efforts to promote and develop IC in biomedical research. She highlighted that the Oviedo Convention of 1997 and its Additional Protocol on biomedical research are the only legally binding instruments in the field that provide a common framework for protection of human rights. She noted that these instruments are a worldwide reference point. In addition, Lwoff explained that the CoE has also adopted a non-legally binding Recommendation on research on biological materials of human origin (CoE, 2016), which provides guidance on implementing IC in biobanking, and an implementation tool to help RECs implement the provisions of the Oviedo Convention and its Additional Protocol.

Lwoff explained that the CoE approaches IC as a process aimed at enabling a person to make an individual choice. IC is the cornerstone of the protection of integrity research participants' rights, and that it imposes a corresponding obligation on researchers not to act against participants' wishes. To make this process possible, she continued, the provision of appropriate information is essential, regardless of the consent system provided for by law and of the format for obtaining consent. In the context of biomedical research, consent must be free, informed, specific and documented. Information communicated to participants must include the envisioned future uses of the research results, data, and/or biological materials.

Lwoff noted that the principle of IC (in research) has been criticised in the recent literature, but argued that while there may be room for scepticism about methods of implementing the IC process, criticism of the value of the process itself is not admissible.

Lwoff presented the Strategic Action Plan on Human Rights and Technologies in Biomedicine for 2020-2025 (SAP), adopted by the DH-BIO in November 2019 (CoE, 2019). The SAP resulted from a two-year analytical process, which was motivated by a feeling in the bioethics community that emerging technologies and the evolution of key practices had presented a turning point for human rights in biomedicine.

Figure 6 - Conclusions of the SAP analytical process

Lwoff summarised the results of this analysis:

1. The key features of new technologies –the speed at which they evolve and the complexity, uncertainty, and difficulty in understanding and anticipating associated risks – call for a new governance model.
2. The emergence of new technologies and the changing demographic context pose significant social challenges for all Member States. Particularly, increasing disparities in access to healthcare are linked to social and demographic changes (e.g. older persons or migrants who have difficulty to access healthcare).
3. Technological developments, especially neurotechnology, genetics and genomics, may pose new risks to the physical and mental integrity of the person.

Lwoff explained that one of the objectives of the SAP is to reconnect biomedical technologies with ethical values and human rights. She argued that governance of new technologies in the biomedical field should be driven by values rather than by potential applications of the technologies. In this regard, the CoE has proposed two actions:

1. To assess whether the existing human rights framework is appropriate to address issues presented by new technologies.
2. To assess the impact of AI in the patient-doctor relationship.

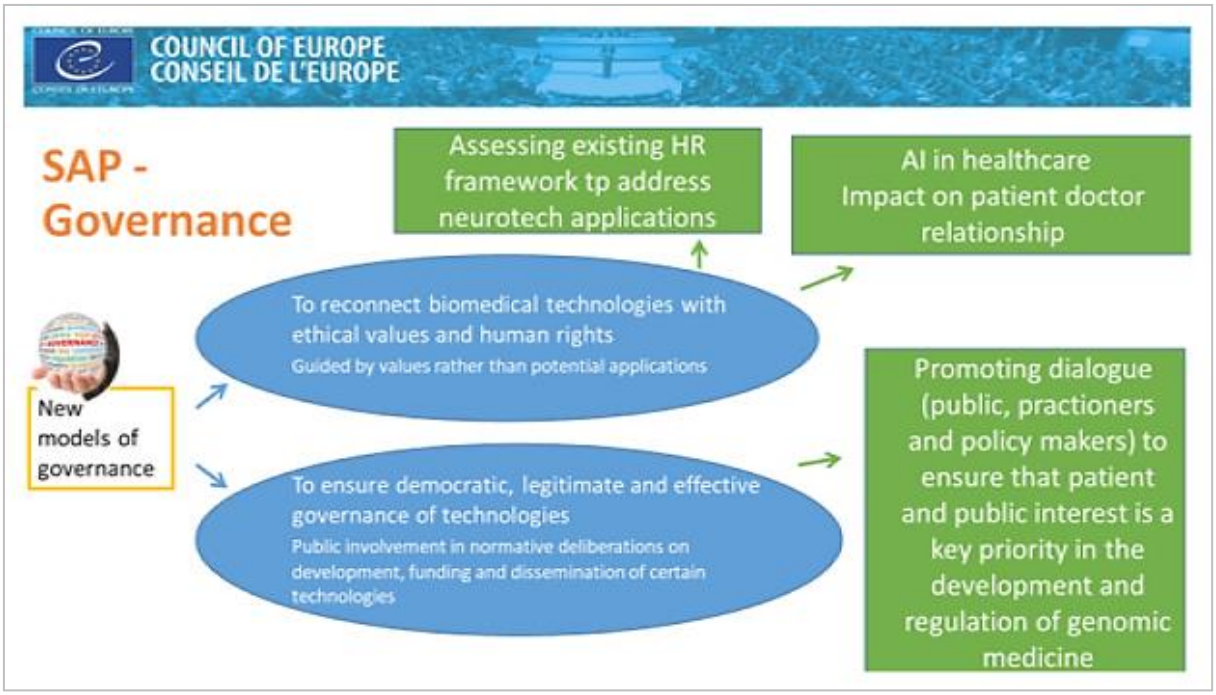

Figure 7 - SAP Objectives in the pillar of 'Governance'

Lwoff insisted on the need to increase trust in science and medicine through sincere consideration of human needs and public expectations. To achieve this, DH-BIO aims to promote stakeholder dialogue to ensure that patient and public interests become key priorities in the development and regulation of new biotechnologies.

Another objective of the SAP is to strengthen children's participation in decision-making regarding their health, and to safeguard their rights in relation to medical practices with long-term implications. Lwoff noted that the outcomes of the i-CONSENT project could inform the work carried out by DH-BIO in this regard.

Discussion

Question / comment: A question was raised about tension researchers face between making information concise and accessible while complying with legal requirements to provide specific, sometimes technical, information to participants, which may not be of interest to the participant.

Presenter response: Lwoff agreed that while enough information must be provided to enable a person to make an informed choice, lack of interest in certain information does not detract from the researcher's obligation to provide it. She suggested using surveys to better understand the level of the information participants would prefer. However, such participant feedback should not be used as an excuse to limit the provision of information that might be necessary for an informed choice to be made. Lwoff added that the answer to the problem should not be to oversimplify information sheets or limit the content to a short list of minimum requirements. The guiding thought should be that participants are taking

part in a process that will enable them to make an individual choice, specific to them; so the type and content of the information they receive should be kept open.

M. Feys: Does the EDPB forces us to come up with another legal ground under GDPR for clinical trials?

Magali Feys, privacy and data protection lawyer and founder of AContrario Law, analysed the impact of EDPB Opinion 3/2019 (EDPB, 2019) on IC in clinical trials. The EDPB Opinion discusses the legal bases for the processing of special categories of personal data within a clinical trial, and for secondary use of clinical trials data for other scientific purposes.

Feys began by highlighting the different aims of the two regulatory frameworks, as noted by the EDPB. The CTR aims to ensure harmonisation of rules for conducting clinical trials in the EU; the GDPR aims to ensure the protection of data subjects and to harmonise rules on the free movement of personal data. She noted that the different aims might lead to a different interpretation of the respective provisions.

Feys pointed out that the aim of the EDPB in their Opinion had been to determine the appropriate legal bases, under the GDPR, by which health-related data could be processed in clinical trials. (The EDPB did not question the validity of IC under the CTR.) Under the GDPR, Feys explained, the processing of health-related data is prohibited under Article 9(1), unless an exemption under Article 9(2) is applicable. She clarified that Article 9(2) applies cumulatively with Article 6, so controllers processing health-related data within clinical trials require an exemption under Article 9(2) *and* a legal basis under Article 6.

Feys explained that the EDPB considers the most likely appropriate legal bases in the context of clinical trials to be:

- the explicit consent of the participant [Art. 9(2)(a), Art. 6(1)(a)];
- the performance of a task carried out in public interest [Art. 9(2)(i)/(j), Art. 6(1)(e)];
- the legitimate interest of the controller [Art. 9(2)(i)/(j), Art. 6(1)(f)].

On explicit consent, Feys recalled the EDPB position that the notion of IC under the CTR must not be confused with the notion of consent as a legal ground for personal data processing under the GDPR: IC under the CTR is founded on core ethical requirements protecting the rights to human dignity and integrity: it is not conceived of as an instrument for data protection compliance.

Feys described two issues noted by the EDPB concerning consent as a legal basis. First, she noted the EDPB's view that, in the context of clinical trials, consent may not always be 'freely given' to the extent required by the GDPR. The EDPB has held that an imbalance of power between the sponsor (data controller) and the research participant (data subject) is liable to occur, as participants are often not in good health, belong to an economically or socially disadvantaged group, or are in a situation of institutional or hierarchical dependency relative to the controller. Second, Feys highlighted the EDPB's observation that the consequences of withdrawing consent differ under the CTR and the GDPR frameworks. Under the CTR, withdrawal of consent does not affect activities already carried out, including the use of data

obtained before consent was withdrawn. However, Feys explained, when consent is withdrawn under GDPR, all processing operations related to the research activities that are grounded on that consent should cease and the data collected should be deleted. This, Feys argued, is problematic for researchers, who are obliged to delete the participant's data even after having achieved results in a clinical trial based on it. Feys noted that this led the EDPB to conclude that, in most cases, consent may not be an appropriate legal basis.

The EDPB, Feys noted, consider legitimate interest a more suitable basis for processing health-related data, except where so doing would threaten the fundamental rights and freedoms of the data subject. Feys suggested that this aspect of the EDPB opinion has not been well received amongst legal experts, partly due to concerns about past misuses of legitimate interest, and partly due to legitimate interest having been misunderstood and underrated as a regulatory mechanism. However, Feys argued, legitimate interest is a perfectly valid ground, requiring controllers to conduct and satisfy a purpose test, a balancing test, and a necessity test[8], and to ensure technical safeguards, such as pseudonymisation.

Feys explained that public interest can also serve as a basis for lawful processing of personal data where this is necessary for the performance of a task carried out in the public interest in the area of public health. However, Feys noted, this basis can be used only where the conditions and purposes of the processing are clearly laid down by national law. Feys stated that the response to COVID-19 by EU Member States presents such a case. She explained that, in Italy, public interest applies as basis for processing health data in emergency clinical trials because the competent authorities enforced an emergency regulation which adopts extraordinary measures to contain the impact of the public health emergency. However, in Belgium, Feys argued, it is not possible as yet to rely on public interest as a lawful ground for data processing in response to COVID-19 because the competent authorities have not passed the necessary legislation.

Discussion

Question / comment: An open question was addressed to Feys, and all other speakers, concerning the level of information that is required to make sure that consent can be considered valid, especially when considering legal obligations to provide certain types of information about the technologies and their governance that can be very technical (e.g. the legal grounds for processing health-related data under GDPR).

Presenter response: The workshop participants agreed that the complexity of the technology and the legal framework that regulates it can undermine participants' trust in researchers and in the study itself. For the system to work effectively, a certain degree of trust must be earned, for example by ensuring that the IC process is as transparent as possible. Feys explained that the principle of transparency under GDPR requires that information, irrespective of its inherent complexity, be given to participants in a manner

[8] Is there a legitimate interest behind this processing? Is the legitimate interest of the controller overridden by the individual's interest, rights, and freedoms? And is the processing necessary to achieve that purpose?

that promotes comprehension, with due regard for the impact of factors such as age, literacy, socioeconomic background, etc.

Lwoff acknowledged that, for research conducted with stored health-related data, the information to be disclosed becomes significantly more complex, as the disclosure of new informational requirements (e.g. communication of the appropriate legal framework for processing their data, legal guarantees, digital risks, secondary and tertiary uses, etc.) becomes a legal obligation. She reiterated that the fact that the information is complex does not affect the participants' rights to know it.

In relation to 'black-box problem' of AI, Ienca argued that communication of this information cannot involve complex explanations of how algorithms work. He suggested that a possible solution would be to provide participants with information about how their information can be potentially accessed. For example, he argued, the principle of auditability could be helpful in these situations, as it requires that algorithms be made auditable and that participants are explicitly informed that these algorithms are amenable to inspection. This, he argued, would increase participants' trust in the data processor.

Concluding remarks

This workshop convened a group of experts to share and discuss challenges to informed consent processes in clinical trials in the digital era. The workshop reflected on themes from the work carried out by AND-CG in the i-CONSENT project on ethical, privacy and data protection issues in this area.

The workshop confirmed the strong influence of technological advancements in biomedical research on the understanding and implementation of informed consent processes. A basic, core challenge is that while transparency requires communication of relevant information to participants in a comprehensible manner, the complexity of technologies such as big data and AI, as well as of regulatory issues around legal bases for data collection, processing, and reuse, makes effective disclosure of key information increasingly difficult, especially for people of lower digital literacy.

At several points in the workshop, participants noted that IC was not originally developed for a digital data ecosystem. We know that, outside of clinical research, the suitability of consent as a primary means of managing personal data processing has been called into question in the scholarly literatures of several fields: might the digitalisation of clinical research lead to a calling into question of the effectiveness of IC as a protection of participant autonomy in the digital era?

The CoE suggests that new technologies are driving biomedical practice and research to a turning point. A new model of governance is required, they claim. The implementation of the SAP may be an opportunity to revisit, and maybe reinterpret, the role of IC. It could be argued that a transformation of IC is already underway, as new adaptive, context-specific models of consent gain support. The workshop participants discussed meta-consent, which may be a promising approach that is respectful of people's rights and interests but which also makes it easier for researchers to access previously collected data in order to pursue societally valuable research goals. Difficulties remain, however.[9]

IC, or at least its implementation, needs to evolve to adapt to digitalisation. This workshop was an opportunity to discuss important ethical challenges in that evolution. For further information about the workshop, the i-CONSENT project, or our research in this area, please contact info[at]and-cg.com.

[9] Some difficulties with meta-consent are discussed in Annex IV.

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Annex 1 | Agenda

10.30 – 10.45	Welcome and introductory remarks **Dimitris Dimitriou**, AND Consulting Group
10.45 – 11.00	Rethinking informed consent: The i-CONSENT project **Javier Díez-Domingo**, FISABIO
11.00 – 11.15	Informed consent in the digital era: Is technology a silver bullet? Ethics and data protection considerations **Silvia Lorenzo-Perez**, AND Consulting Group
11.15 - 12.30	**Session 1** - Perspectives on the future of consent in clinical research
	Moderator **Sally Jackson**, Ospedale Pediatrico Bambino Gesù Presenters **Søren Holm**, University of Manchester *Consent solutions for secondary use of trial data after the end of the trial* **Marcello Ienca**, ETH Zurich *The implications of big data for informed consent*
12.30 -13.15	Lunch
13.15 -14.30	**Session 2** - The European regulatory landscape for consent in clinical research
	Moderator **Silvia Lorenzo-Perez**, AND Consulting Group Presenters **Laurence Lwoff,** Committee on Bioethics of the Council of Europe (DH-BIO) *Informed consent -Council of Europe reference work and new challenges* **Magali Feys,** Acontrario Law *Does the EDPB forces us to come up with another legal ground under GDPR for clinical trials?*
14.30 – 15.00	Open discussion
15.00	Adjourn

Annex 2 | List of participants

Name	Affiliation
Böröcz, István	Vrije Universiteit Brussel
Díez-Domingo, Javier	FISABIO
Dimitriou, Dimitris	AND Consulting Group
Dobreva, Dafina	FISABIO
Feys, Magali	AContrario Law
Fons, Jaime	FISABIO
Garcia-Bayarri, Julia	FISABIO
Holm, Søren	University of Manchester
Ienca, Marcello	ETH Zurich
Jackson, Sally	Ospedale Pediatrico Bambino Gesù
Lorenzo Perez, Silvia	AND Consulting Group
Lwoff, Laurence	Committee on Bioethics of the Council of Europe
Miller, Kristen	N/A
Roda, Sara	Vrije Universiteit Brussel
Tozzi, Alberto	Ospedale Pediatrico Bambino Gesù

Annex 3 | Speakers' biographical notes

Magali FEYS
Acontrario Law

Magali Feys is a privacy and data protection lawyer who founded two years ago AContrario Law. AContrario Law is a boutique law firm specializing in IP, IT, Data Protection and Cybersecurity related matters, not only from a legal but also from a technical perspective. In addition, Magali is a member of the legal working party e-Health of the Belgian Minister for public healthcare. This Working Party advices the minister on the different legal aspects relating to the e-Health Plan and the use of health data. Magali is also active as a business coach at Imec.Istart, BlueHealth Innovation Center and Vlerick Business School where she regularly gives workshops on IP, IT, Data Protection and AI.

Søren HOLM
Centre for Social Ethics and Policy, University of Manchester

Søren Holm is a medical doctor and philosopher. He is Professor of Bioethics at the University of Manchester and Professor of Medical Ethics (part-time) at the University of Oslo. At Manchester University he is the Academic Director of Research Governance, Ethics and Integrity. He has been researching issues around consent to biomedical research since the early 1990s and has together with Professor Thomas Ploug, Aalborg University developed 'Meta-consent' as a flexible approach to the secondary use of research and clinical data.

Marcello IENCA
Department of Health Sciences and Technology, ETH Zurich

Marcello Ienca is a Senior Research Fellow at the Department of Health Sciences and Technology at ETH Zurich, Switzerland. His research focuses on the ethical, legal and social implications of neurotechnology and artificial intelligence, with particular focus on big data trends in neuroscience and biomedicine, human-machine interaction, social robotics, digital health and cognitive assistance for people with intellectual disabilities. He is interested in comparative approaches to the study of human and artificial cognition. Ienca is the Principal Investigator of multi-disciplinary federal research projects and has received several awards for social responsibility in science and technology such as the Prize Pato de Carvalho (Portugal), the Vontobel Award for Ageing Research (Switzerland), and the Paul Schotsmans Prize from the European Association of Centres of Medical Ethics (EACME). Ienca is serving as appointed member or expert advisor in a number of national and international governance bodies including the Steering Group on Neurotechnology and Society of the Organisation for Economic Co-operation & Development (OECD) and the Council of Europe's Ad Hoc Committee on Artificial Intelligence.

Laurence LWOFF
Committee on Bioethics of the Council of Europe (DH-BIO)

Mrs Laurence Lwoff holds a MSc in reproductive physiology from the University of Paris VI – Jussieu (France). She then obtained her degree in agronomy from the Institut National

Agronomique Paris-Grignon (France) in 1986 and received her PhD in molecular biology in 1989. She joined the Council of Europe in 1991, where she was entrusted with the responsibilities of the Secretariat of the Conventions concerning the use of animals in agriculture and science, in the Directorate of Legal Affairs. In 1999, her responsibilities were extended to biotechnology. She was the Secretary of the International Conference of the Council of Europe on Ethical Issues Arising from the Applications of Biotechnology (Oviedo, Spain, May 1999). In 2002, she joined the Bioethics Department where she has been responsible in particular for the activities on human genetics and on the protection of the human embryo and the foetus. She was the Secretary of the Group in charge of the elaboration of the Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes. She is currently the Head of Bioethics Unit (DGI - Human Rights Directorate) and Secretary of the Committee on Bioethics (DH-BIO), intergovernmental committee in charge of the activities on the protection of human rights in the biomedical field, at the Council of Europe.

Annex 4 | Scene-setting report

Ethical, privacy, and data protection issues associated with the use of ICT for obtaining informed consent

Today's online session is organised by AND Consulting Group within the scope of the **EU-funded research project 'i-CONSENT'** (full title: *Improving the guidelines for informed consent, including vulnerable populations, under a gender perspective*).[10]

1 Introduction

Though guidelines on informed consent (henceforth 'IC') differ somewhat in details or emphasis, they share a common thought: that through the IC process all relevant information about the study should be disclosed to the prospective participant; that the participant should adequately understand the information (disclosure); and that the participant should have the capacity not only to comprehend the information (capacity), but to knowingly and voluntarily agree to take part in the study (understanding, voluntariness), under the conditions disclosed to them (cf. Beauchamp & Childress, 2009).

In i-CONSENT we identified several challenges to this traditional approach to IC. Here, in no particular order, are a selection:

- The attempt to ensure transparency and openness about a study can lead to lengthy and complex paperwork (as can a desire to limit legal liability). IC forms can thus be unpleasant to read and difficult to understand.
- There is a lack of established ethical or legal standards for determining how participants' specific characteristics should influence the way in which key information is disclosed to them.[11] Barriers to comprehension include: age and other demographic factors; education levels or literacy; and cultural differences in attitudes to and understanding of risk (Meade, 1999).
- Variations of, e.g., culture give rise to variation in the way that participants perceive or evaluate the IC process. Should different groups be subject to different IC procedures? To what extent should information be tailored to individuals?
- People's identities and circumstances are always multifaceted. One may be a member of many groups with various attitudes towards, say, autonomy. If different

[10] The i-CONSENT consortium comprises 7 partners (including academia, research centres, industry, patient organizations and small and medium-sized enterprises) from 4 countries. The project is funded by the European Union under grant no. 741856.

[11] This is not to say that such standards do not exist at all; only that there are many specific contexts in which they do not deliver decisive and unambiguous recommendations.

groups receive different IC approaches, how does this speak to broader societal questions of inclusion and integration?

- Translation of IC forms and other paperwork can be problematic. Since information delivery is context- and norm-dependent, and since it really matters *how* you say something (Manson & O'Neill, 2007), translations can easily misfire.
- Participants and researchers are subject to implicit biases. Researchers may manifest bias in recruitment, favouring those they find easier to communicate with. Researchers and participants may manifest *optimism bias* (see, e.g., Miller & Joffe, 2013; Pentz et al., 2012): researchers may overemphasise potential benefits; participants may be subject to *therapeutic misconception* (Appelbaum & Lidz, 2008), i.e. the false supposition that involvement is likely to have a therapeutic benefit.
- Information overload can be a trigger to biases. The coping heuristics to which one often reverts when faced with a large volume of information are liable to harbour deep-seated biases. The trouble with lengthy and complex paperwork is not only comprehension, but that the most natural ways of attempting to process them are likely to introduce, embed, or trigger biases.
- Protection of participants' personal data is paramount, especially given the sensitive nature of health-related data (a 'special category' of personal data in the *General Data Protection Regulation 2016* (henceforth '*GDPR*').
- Confidentiality is crucial, especially for vulnerable people (e.g. compare a minor's right to privacy and a parents' interest in the minor's health). A related important issue concerns incidental findings. Where these impact a participant's health, the participant should be informed if they wish (*The Oviedo Convention 1997*, Article 26). But the issue intersects with others, including the rights of 'secondary subjects'.
- Confidentiality and data protection also concern secondary uses of previously collected data or biological samples. These can be hugely scientifically valuable but must be legally sound and suitably approved by a research ethics committee (REC) or institutional review board (IRB) (cf. issues of health databases and biobanking).

The central objective of i-CONSENT is to reflect on these kinds of problems and to develop guidelines for improved IC practices in clinical research. As part of this work, AND Consulting Group produced a report examining **ethics, privacy, and data protection issues raised by the use of ICT, technology, and innovative techniques to overcome the traditional barriers to effective IC processes**. The present document describes some of the findings of that report and is offered here as background to the online event to which you have been invited.

2 Technologies and techniques

Our main goal is to understand how proposed innovations to the IC process might improve, or worsen, the protection of the rights and interests of the participants.

We identified four main categories of intervention: the use of 'enhanced' IC forms; the use of multimedia, including video, interactive web-based or electronic device-based tools,

and e-consent; the use of online systems for facilitating a version of 'dynamic consent'; and the provision of dedicated training to researchers in IC.

(a) Enhanced informed consent forms

A number of studies suggest that various *non-technological* steps could serve to improve the readability and comprehensibility of IC forms.[12] These include making consent forms simpler and shorter; using lay terms and a glossary for unavoidable technical terms; using layered or tiered approaches; using visual supports to communicate key information; and tailoring information to different groups (Jimison et al., 1998, p. 250).[13] Despite an absence of decisive evidence in support of enhanced informed consent forms (Flory & Emanuel, 2004), most scholars who comment tend to offer them (at least tentative) endorsement (e.g. Flory et al., 2008).

(b) Multimedia tools (touchscreen, web, video, audio, etc.)

Here we consider multimedia techniques, i.e. those attempting to improve the informed consent process by using more than one means of presenting information to participants. Approaches that are structured and modular, with use of video and audio, can make the information far more accessible and tend to decouple comprehension from literacy or education level (Jimison et al., 1998, p. 250). These approaches allow the participant to review information as often as they need, and via the media with which they are most comfortable (Batuyong et al., 2014). In some cases, the participant's use of the tools can be monitored, which can support better assessment of their comprehension.

Interactive tools may offer additional benefits. Tait et al. (2012, p. 43) argue that interactive ICT-based media promote active participation. This is thought to enhance comprehension (Lorrell et al., 2015, p. 693). In general, moving away from passive models wherever possible has potential value in terms of other social goods, including health literacy and citizen engagement with health resources (Mullins et al., 2014).

Multimedia approaches lend themselves to 'e-consent', i.e. "IC that is interactive, delivered via electronic media, and may contain multi-media functions" (Lentz et al., 2016, p. 68). Besides advantages in terms of participant engagement and comprehension, e-consent and multimedia enable streamlining of administrative aspects of IC, by, e.g., reducing paperwork and minimising data entry tasks (Madathil et al., 2013, p. 855).

[12] For example, Dunn & Jeste, 2001; Tait et al., 2005; Appelbaum & Lidz, 2008; Lorrell et al., 2015.

[13] Bossert & Strech (2017) highlight the importance of involving members of the target population, and other stakeholders or experts, in the development and testing of an informed consent process.

(c) Dynamic consent

If IC is a process then there must be means of accommodating changes in information, or perception of or attitudes towards, information during that process. Dynamic consent platforms, which were originally developed in relation to biobanks, can play this role. Dynamic consent provides "an interactive IT interface to engage with participants, [... which] enables participants to consent to new projects or to alter their consent choices in real time as their circumstances change" (Kaye et al., 2015, p. 142).

A platform can also serve as a source of information (ibid., p. 143) and may offer opportunities for improving the all-round management of a clinical trial, enhancing patient recruitment, enrolment, encouraging retention, supporting data collection, and long-term follow-up evaluation" (Covington & Veley, 2014; Bailey et al., 2013).

(d) Training for researchers / healthcare professionals in IC

Issues that healthcare professionals have to communicate are often complex and difficult to explain in lay language. Training in communicating such ideas is important (European Science Foundation, 2012). The importance of training is also emphasised in the *Declaration of Helsinki 1964/2013* (Article 12), as well as CIOMS Guideline 1: "Sponsors, researchers, and research ethics committees must ensure that all research personnel are qualified by virtue of their education and experience to perform competently and with integrity. This includes receiving appropriate ethics education and training".[14]

Butow et al. (2014, p. 2570) found that while training can improve the IC process, "methods to increase the impact of training are required". McEvoy et al. (2016) found that a mobile phone app could be used to present guidelines to physicians and improve their adherence to the guidelines in clinical settings. They also found that digital natives *expect* the use of tools such as smartphone apps as they increasingly relying on information retrieval rather than memorisation (ibid., p. 192).

3 Ethical issues

The central way in which the IC process goes wrong – either by lack of care or simply because it is inherently difficult – is by failing to adequately support researchers in providing, and participants in gaining, genuine comprehension of the key facts about participation in a trial. Technology-supported approaches can address this problem, at least to some extent. But the use of technology raises concerns. These are discussed at length in our full report. We here summarise (in no particular order) some of the key issues.

(a) Importing existing problems of consent in an online world

Though online technologies offer potential solutions to some problems in IC, we must not forget that they bring problems of their own.

Agreements to consent, given online, are often problematic. As Frischmann (2019) emphatically puts it: "electronic contracting and the illusion of consent-by-clicking are a

[14] See also *Guideline for Good Clinical Practice* (ICH, 1996, §2.8) and the *Universal Declaration on Bioethics and Human Rights 2005* (Article 23).

sham". The field of IC in healthcare is arguably better equipped in this respect: after all, projects such as i-CONSENT only get going at all because it is recognised that there are serious concerns about ensuring that people are genuinely informed before taking important decisions about healthcare or clinical research. But can we be confident that this distinction is robust for the long-term?

The online and offline realms are no longer distinct, but overlap, interlace, and ultimately meld. This is the "onlife experience" (Floridi, 2013). Rapid development of ICTs and big data processing make it extremely difficult – probably impossible – to *fully* inform people of the uses to which their data may later be put, or to guarantee the effectiveness of anonymisation of health data. Technological developments in IC must be adaptive to future trends in the exploitation of health data (Ploug and Holm, 2015a).

A further problem concerns not only *how* consents are collected online, but *how often* they are. 'Consent fatigue' (Kaye et al., 2015) and 'routinisation' (Ploug & Holm, 2013; 2014; 2015b) are real and have consequences. How often, then, should a participant be requested to renew or reconfirm their consent to participation in a clinical trial? One clear risk is that the seriousness of the decision to continue in a clinical trial could be made to seem diminished by its being signalled by a process (e.g. clicking on a button on a website) that is mundane, routine, and frequently done with relatively little thought for the consequences.

Finally, what of security issues? Who should be responsible for the security of, say, a website providing 'always available' information about a trial? Who should be responsible if that website is hacked and the information rendered unavailable, or changed, or links to supporting information maliciously altered? (It is not difficult to imagine this sort thing occurring in more socially, culturally, or politically charged domains such as vaccination.)

(b) Respect for autonomy and protection against harm

Autonomy is one of the key concepts in IC. How might the use of technology in the IC process affect respect for participants' autonomy?

The use of technology can be seen as promoting the autonomy by helping participants to better understand key facts about a trial. This assumes a view of autonomy according to which autonomous decisions are founded on education, understanding, and rational capacity. On this view, the support that subjects receive from researchers when making their decision to consent is not a paternalistic affront to their autonomy, but rather a reinforcement of the foundations of their autonomy (relative to the decision in question).

But we must here acknowledge a difference between technologies or techniques that serve to provide better quality information to subjects (or to provide information in a more comprehensible way), and technologies that have the effect of distancing the subject from the researcher. The latter may include online platforms, resources, or forums, in which potential participants can explore information about a clinical trial on their own. Such resources may be extremely effective (thought the evidence is not clear). But they must be implemented in the right way. They should not be associated with a view of the decision-maker as wholly independent of the researchers. Such views, which wrongly equate autonomy with independence, may promote negative ethical outcomes if they put too great

a burden on the subject to be wholly responsible for coming to his or her decision (cf. The European Group on Ethics in Science and New Technologies, 2015, p. 62).

The potential role of *nudging* in IC is quite striking. Knowing, for example, that potential participants are prone to certain kinds of bias or misunderstanding, the choice architecture can be tailored to make certain options or aspects appear more salient. The obvious objection to this kind of approach is that it may be a manipulative affront to autonomy.[15] But it may be countered that, in a controlled and well-governed context, nudging in IC need not necessarily be more manipulative than any other intervention. All transmission of information involves choices about the mode of communication. Manipulating the choice architecture does not *have to be* equivalent to manipulating the chooser, or so the claim goes.

Perhaps we may at least say that while nudging in the IC process is not *inherently* manipulative in a problematic sense, this is not to say that it *cannot be* problematically manipulative. In general, there must be careful attention to the use of technologies in the IC process, not only to understand how decisions taken regarding their configuration might influence participants in their decision-making processes, but also to understand what 'configurations' are built-in to their design.

(c) Monitoring comprehension

Technological innovations in the area of IC focus mainly on enhancing the means of presenting key information. Many studies have indicated that interactive platforms could potentially be used to monitor, test, or evaluate participants' comprehension. Jimison et al (1998), e.g., used a platform which recorded which topics participants had viewed and later prompted them to view any unseen topics before they could proceed to the next step; they also included self-test modules that could prompt the user to review specific information.

Such innovations, if they are to be effective, must be relatively unobtrusive. If not, they will be felt as a burden, or source of pressure or other discomfort (Anderson et al., 2017). Technology now makes it easier than ever to record patients' tests, system navigation histories and habits, and other indicators of comprehension in an unobtrusive manner. But with this positive possibility comes potential concerns, particularly about privacy. In an online environment, such monitoring would likely be compared to other forms of online surveillance (many of which are highly pernicious). This may undermine trust.

(d) Personalisation and discussion

The clearest and least equivocal recommendations stemming from the literature concern personalisation of the IC process and the importance of discussion between the researcher and the participant. In the context of telemedicine – which, in this regard at least, is analogous – the World Medical Association says that "Face-to-face consultation between physician and patient remains the gold standard of clinical care" (*WMA statement on the ethics of telemedicine 2007/2018*, preamble).

[15] See, e.g., Holm & Ploug, 2013; Wilkinson, 2013; see also Blumenthal-Barby, 2013; Grüne-Yanoff & Hertwig, 2016; Simkulet, 2018.

Technology can clearly support approaches emphasising discussion and interaction since it promises to both increase the comprehensibility of the information on which the discussion and interaction are based, and also to make remote interaction easier and cheaper. But it is clear that these measures must be supports – rather than alternatives – to the face-to-face discussion. There can be some reluctance to place too much emphasis on the discussion part of the IC process. This is due to a concern that, being more 'free-form' than, say, a written information sheet, it is more difficult for IRB/RECs to review. But this in no way negates the obligation to provide a personalised approach.

Personalised discussions are of importance for two key reasons. First, being *personalised*, there is greater scope for investigating issues arising from the idiosyncratic background of the individual participant. Second, being *discussion-based* lends the process a flexibility that can be difficult to imitate in static media. A degree of interactivity is required to genuinely engage the subject. Engagement is key for comprehension (Lentz et al., 2016, p. 67).

Moreover, the discussion brings an essential human element to proceedings. This is essential for at least three reasons. First, in a face-to-face discussion, the subject is more likely to develop a trusting relationship with the research team (Walsh & Sheridan, 2016; Thiel et al., 2015; Anderson et al., 2017). Second, notwithstanding the inherent difficulty of coming to know what a given individual needs (Israel, 2015, p. 80), humans are better able to do this than technology. A properly trained research team member is far more likely than the 'self-test-module' of an interactive IC system to detect when a subject feels uneasy or uncertain about a topic (certainly, a human is more likely than a machine to distinguish between a participant's guesses and confident responses to questions). Third, there must be scope for providing all appropriate support to individuals who cannot, or simply do not wish to, engage with the technology.

Amid all the positive potential, one issue to consider is whether the use of such tools as email, VoIP, messaging services, social networks and online forums might introduce risks or negative consequences. It is possible for such technologies to have a distancing effect. But there are obviously pros and cons to consider. Distancing effects may be offset by the greater number of meetings made possible (online meetings requiring far fewer resources for both parties). It should also be said that, in some cases, distancing may be welcome if, for instance, the discussants find that the distance engenders a less intimate space in which it is easier to be open about one's thoughts and feelings.

(e) Trust (in the technology)

Assurance of the identity of the researchers and participants in online or otherwise remote interaction is critical to the whole process (Thiel et al, 2015): "The patient-physician relationship must be based on mutual trust and respect. It is therefore essential that the physician and patient be able to identify each other reliably when telemedicine is employed" (WMA Statement on the Ethics of Telemedicine 2007/2018, §2).

In some cases, it may be preferable to allow for anonymous, or at least pseudonymous, interaction. In online forums, it may be best to allow participants to interact under a pseudonym. By contrast, there seems no good reason to allow for anonymous or pseudonymous contributions from the research team (to ensure accountability).

Researchers should follow the guidance provided in the *WMA Statement on the Professional and Ethical Use of Social Media 2011* regarding conduct on social media, extrapolating to similar environments.

Trust in technology is partly underwritten by technical standards. The development of standards must be inclusive and transparent, for they are not neutral, but "embody choices (ethical, social, economical, political, epistemological, …) of their creators and will necessarily favour particular views of patients or diseases while excluding others" (The European Group on Ethics in Science and New Technologies, 1999, p. 6).

(f) Lessons from biobanks and health databases

The most prominent challenges concerning consent in the context of biobanks and health databases typically concern future uses of subjects' data. Thus Article 12 of the *WMA Declaration of Taipei on Ethical Consideration Regarding Health Databases and Biobanks 2002/2016* sets conditions for the validity of consent to future uses of data. It includes requirements that the subjects be "adequately informed" about a range of issues, including the purpose of the biobank or health database, risks associated with the data processing, privacy protection, and the governance of the biobank or health database. These are a useful guide for conditions on validity of consent to clinical trial participation, managed in similar technology-based contexts by dynamic consent systems.

Good governance and oversight of a dynamic consent system will encourage confidence and trust: poor governance and oversight may have the opposite effect. An IRB/REC should approve any system that is deployed, ensuring that it is so set up as to enable participants to adequately monitor progress in the trial, be informed of important developments or changes, and modify their consent preferences if necessary. Article 20 of the *WMA Declaration of Taipei on Ethical Consideration Regarding Health Databases and Biobanks 2002/2016* sets out four principles of good governance:[16]

- *Protection of individuals*: Governance should be designed so the rights of individuals prevail over the interests of other stakeholders and science.
- *Transparency*: Any relevant information on Health Databases and Biobanks must be made available to the public.
- *Participation and inclusion*: Custodians of Health Databases and Biobanks must consult and engage with individuals and their communities.
- *Accountability*: Custodians of Health Databases and Biobanks must be accessible and responsive to all stakeholders.

The same holds true, *mutatis mutandis*, of a dynamic consent system. But, that being so, the associated difficulties carry over too. For instance, EU DG Research and Innovation (2012, p. 8) note a serious practical difficulty with biobanks in Europe: "Most Europeans have never heard about biobanks". Principles like *transparency*, *participation and inclusion*, and *accountability* are therefore not easily translated into effective practical governance

[16] Article 21 of the *WMA Declaration of Taipei on Ethical Consideration Regarding Health Databases and Biobanks 2002/2016* describes further, more specific, issues to be addressed through the governance structure.

measures due to relatively low digital-health-literacy levels (in this area). Dynamic consent systems are likely to face a similar challenge.

(g) Broad consent vs. dynamic consent

The standard approach to consent in the context of biobanks has been *broad consent*. On this model, the subject donates their biological material or data to the biobank and gives consent *to a certain kind of* future research (subject to coding or anonymisation, good governance of the resource, oversight from ethics boards, and so on).

A number of concerns have been raised about broad consent, often concerning confidentiality, privacy, and data protection. Measures like coding and pseudonymisation do not put data beyond all possibility of reidentification, especially in the era of big data. Yet we should not be dismissive of broad consent. It is "a practicable way of implementing consent for open ended projects" and "protects society's interest in research" in a context where "the practicalities of getting full informed consent for every secondary use of data will hinder research" (Ploug & Holm, 2015a).

This forms the basis of a critique of dynamic consent (Ploug & Holm, 2015a), which transfers across to its potential use for IC in clinical trial contexts. First, it does not sufficiently protect society's interest in research because, if people are asked to consent to every secondary use of their data, statistics suggest that they will not consent as often as is societally desirable. Second, although dynamic consent aims to promote genuinely informed consent,[17] subjects could potentially receive so many requests for consent as to engender 'consent fatigue' (Kaye et al., 2015, p. 143) and 'routinisation' (Ploug & Holm, 2013; 2014; 2015b), robbing it of its capacity to protect and promote autonomy.

In response to these concerns, Ploug and Holm (2015a) propose a third option: *meta-consent*. Here, participants "choose how they wish to provide consent for future secondary research of data collected in the past or of data that will be stored in the future". Budin-Ljøsne et al. (2015) suggest that, rather than promoting autonomy, meta-consent may in fact undermine it, arguing, in effect, that taking broad consent to a meta level does not address its shortcomings (e.g. in terms of individuals providing consent to future, as yet unknown, uses of their data). A further point to add is that both broad consent and meta-consent are, *prima facie* at least, inconsistent with the Good Clinical Practice definition of *informed consent*, which refers to a subject's voluntary confirmation of their willingness to participate in a *particular* trial (ICH, 1996, §1.28).

Nonetheless, while broad and meta-consent may be problematic for their own reasons, the critique of dynamic consent – that it may play in to consent fatigue, routinisation, and not best serve societal interests in health research (which is rather topical at the moment) – cannot be ignored. Any technological platform for IC should be designed with the key points of this debate in mind. The system must be developed in such a way that it facilitates the kind of ongoing dialogue and potential to review and reaffirm (or withdraw) consent that respect for the individual participant requires, but it should at the same time not

[17] This is in contrast to broad consent, which is argued not to allow for genuinely informed consent: "Opponents argue that broad consent is not necessarily informed consent because informed consent requires specific information about the research for which the data or tissue may be used" (Ploug & Holm, 2015a).

overload the participant with updates and requests for renewed consent that could lead to consent fatigue or routinisation. This is an extremely delicate balance. And it may require a different balance for different people.

(h) Quality of information

How can it be ensured that participants get access to good quality, reliable information; and how can it be ensured that they are not exposed to poor quality, unreliable information? There is plainly a risk of unreliable information entering into the mix – whether from the Internet, or pressure groups, or just unfounded gossip – and contaminating the deliberation procedure for participants considering whether or not to take part in a clinical trial. Information and, more pertinently, misinformation, about vaccinations are a topical case in point.

It is important, therefore, that if information about a clinical trial is to be presented online, it should be presented in ways that generate (well-founded) trust in it: "It can be difficult for patients to judge the quality of the information presented on the many websites that offer health information and advice, and patients can also experience difficulties in putting the information into the context of their specific clinical situation" (The European Group on Ethics in Science and New Technologies, 2012, p. 52).

Whatever the approach, the goal should be that the participants using that resource are rightly confident that what they there learn is reliable. Similarly, if resources allow for interaction between participants (e.g. between people currently enrolled and people considering enrolling) are provided, it should be ensured that the information passing between them is reliable (this may be more or less challenging depending on the medium). More generally, it may be that in providing information to potential participants, it is necessary to also provide information on where else to source reliable information, and how to spot the signs of unreliable information or fake news (Waldrop, 2017; Scheufele & Krause, 2019; Charlton, 2019). Participants may need to be educated in such matters: it is highly unlikely that many adults today were taught such things at school.

It may not only be information about the health or medical aspects of the study that require attention. It may be that information or misinformation about the organisations sponsoring or conducting the research is available online. Managing this information is rather sensitive as, poorly handled, it may look like whitewashing; on the other hand, foregrounding positive opinions, even if well-earned and justified, may appear as grandstanding or coercive. As in all aspects of the IC process, it is important to provide high quality, accurate information, to resolve misinformation where possible, and to foster a trusting relationship between the research team and the participants.

(i) Technology and IRBs/RECs

One of the challenges of introducing technology into the IC process is to ensure that IRB/RECs are satisfied that they are able to adequately assess the implications of it. The focus groups with former clinical trials participants and research team members conducted by Anderson et al. (2017) revealed a concern that IRB/RECs would be less open to innovative approaches, given their necessarily limited track-record and unfamiliarity with such approaches, and that this could stifle innovation overall.

(j) IC and data protection: the CTR vs. GDPR controversy

The European Data Protection Board (EDPB) recently issued an opinion on the appropriate legal basis for the processing of personal data in the context of clinical trials and on secondary use of clinical trials data for other scientific purposes (European Data Protection Board, 2019). For present purposes, the key point to note is that, according to the EDPB, the notion of IC referred to in the *CTR* must not be confused with the notion of consent specified as a potential legal ground for personal data processing under the *GDPR* (at Articles 6-7). The notion of IC under the *CTR*:

> Respond[s] primarily to core ethical requirements of research projects involving humans deriving from the Helsinki Declaration. The obligation to obtain the informed consent of participants in a clinical trial is primarily a measure to ensure the protection of the right to human dignity and the right to integrity of individuals [...]. [I]t is not conceived as an instrument for data protection compliance. (European Data Protection Board, 2019, para. 16)

Consent under the *GDPR* serves the purpose of protecting the individual's personal information, which is why, according to the *GDPR*, consent to the processing of health data must be given freely, and must be specific, informed, unambiguous and *explicit* (European Data Protection Board, 2019, para. 17). To assess the validity of the consent to personal data processing, controllers should verify that all conditions of valid consent, as defined at *GDPR* Article 7 and the *Working Party 29 guidelines on consent* (Article 29 Working Party, 2018), are satisfied in the context of the specific clinical trial (European Data Protection Board, 2019, para. 17). Here, the idea of *freely given consent* is critical:

> The EDPB considers that data controllers should pay particular attention to the condition of a 'freely given' consent. As stated in the Working Party 29 Guidelines on consent, this element implies real choice and control for data subjects. Besides, consent should not provide a valid legal ground for the processing of personal data in a specific case where there is a **clear imbalance between the data subject and the controller**. (EDPB, 2019, para. 18)

Summarising, the implied argument runs as follows.

(1) The existence of an imbalance of power between a data subject and data controller may challenge the reliability of consent as a legal basis for the controller's processing of the subject's personal data.

(2) In the context of clinical trials, an imbalance of power between the sponsor (data controller) and the research subject (data subject) is liable to occur, given that, often, participants are not in good health, belong to an economically or socially disadvantaged group, or are in a situation of institutional or hierarchical dependency relative to the controller.

(3) Therefore, in the context of clinical trials, consent may be an unreliable legal basis for the controller's processing of the subject's personal data.

While the *CTR* does consider this imbalance of power, it merely requires sponsors to *take into account* all circumstances which might influence the decision of a subject to participate

in a clinical trial when obtaining IC (see *CTR*, Recital 31). The provision in this recital is, *prima facie*, less stringent than that adduced by the EDPB. It demands that account be taken of power imbalances: but the EDPB go further in clarifying that, for the purposes of the personal data processing, these power imbalances are decisive in invalidating the data subject's consent. For this reason, the EDPB advises that controllers: "conduct a particularly thorough assessment of the circumstances of the clinical trial before relying on individuals' consent as a legal basis for the processing of personal data for the purposes of the research activities of that trial" (European Data Protection Board, 2019, para. 21).

The Opinion is consequential for the overall IC process because it brings out the complexity of processing personal data in the context of clinical trials. It is already difficult to explain the details of what data will be collected and its subsequent life-cycle. A consequence of the EDPB opinion is that explaining the technical details – in particular, the legal basis upon which personal data is processed – in simple language is considerably more difficult.

Further complications can be imagined in cases where ICTs are used as part of the recruitment and informed consent process. It is not clear how the EDPB Opinion relates to the use of such tools. Presumably, if consent is not a viable legal basis for personal data processing within the context of the trial due to an institutional power imbalance between the subject and the controller, it cannot be a viable legal basis for *any* personal data processing agreement between that subject and that controller. This could lead to the following almost paradoxical position concerning dynamic consent.

Suppose that a person had enrolled in a dynamic consent platform and had submitted various preferences for consent in different circumstances. As discussed above, it has been proposed that in order to avoid issues such as 'consent fatigue' and 'routinisation', a system of dynamic consent should include elements of broad consent. Thus, participants will have the opportunity to consent to participate (or have their data used for) all trials of a certain kind. This means that, other things being equal, they will not be asked to provide consent for these future trials. Suppose now that in the 18 months between the subject originally submitting their consent preferences and the current time, the subject has become seriously and chronically ill. Suppose further that, at the later time, the subject is in a situation of institutional or hierarchical dependency relative to the controller. Now, in some sense, the subject's changed status relative to the controller need not be problematic. Let us stipulate that the controller had carefully considered the EDPB Opinion and decided not to rely on consent as a legal basis for data processing. Since the processing of the subject's personal data was not based on consent, their changed status vis-à-vis the controller does not affect the legal basis. Moreover, as we have seen, the *CTR* does not exclude the possibility of valid IC even in cases of institutional or hierarchical dependency. However, even granting this much, a problem still emerges.

The subject is presumed to have given consent to participate in a new clinical trial based on their previously stated preferences, recorded on the dynamic consent platform. But, on a plausible reading of the EDPB Opinion, the subject is now in such a position vis-à-vis the controller that they are not able – due to institutional or hierarchical dependency relative to the controller – to provide valid consent to any processing of personal data. *A fortiori*, if the subject had not already subscribed to the dynamic consent platform, they would not

now be able to. So, the subject is to be enrolled in a new clinical trial based on personal data (i.e. a previously stated consent decision) which, if it had not *already* been collected, *could not* now be legitimately collected. Now this is not to say that the subject has changed their mind or withdrawn their consent (they may very well still have *exactly the same* consent preferences as are recorded in the dynamic consent system). The problem, rather, is that the subject is not, in the eyes of the EDPB, in a position to use the dynamic consent system; and that surely calls into question the legitimacy – ethically, if not legally – of relying on consent decisions stored therein. We find this puzzling.

4 Invitation to discussion

We invite you reflect on the issues raised above and to bring your particular perspectives and expertise to the discussion in our online session.

This document is drawn from a full report, developed by AND Consulting Group in the scope of the i-CONSENT project. The full report includes risks and recommendations concerning the use of technology and new techniques to enhance the IC process. If you would like to see the full report, please contact us at info@and-cg.com.

Further information about the i-CONSENT project can be found online: https://i-consentproject.eu/.

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