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Abstract:	This Deliverable responds to the requirement stemming from ethics review and subsequent ethics check that, "A document with standard procedures for consent and templates for information sheets must be developed and must be submitted to the EC". This deliverable 'SOP' is a set of conditions for making consent forms in the HBP. It lays out the material that HBP researchers need to create their research-specific information sheets and informed consent forms, in the contexts of their legal and institutional settings. This single point of reference for H2020 regulation (and beyond) is the most ethically efficacious means of providing consistent compliance for this area.
Keywords:	Ethics, Informed Consent, Incidental Findings

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1. 1 Introduction

This document provides a set of minimum required standards and procedures for informed consent (IC) to be obtained by researchers in the Human Brain Project. These standards and procedures must form the basis of HBP IC. These criteria constitute a standard operating procedure (SOP) by setting out clearly what is expected of HBP researchers with regard to IC, as well as the roles of the Ethics Management and Ethics Advisory Board in this area.

A single template covering all stakeholders' requirements on IC is not feasible given the diversity of HBP research areas and practices, as well as national and institutional variations in procedures, and in the structures for local ethics bodies. For this reason, this SOP does not prescribe IC documentation in detail. Rather, it sets out a format for what is required of such documentation for HBP purposes. Principal Investigators (PIs) and task leaders will be expected to look at their own research activities, especially in the light of the H2020 self-assessment criteria, and ensure that their IC approach and documentation are consistent with the relevant requirements of this document.

Not all elements of every section of the SOP might be relevant for the particular research activities undertaken -- this is an SOP aiming to cover a multitude of activity. PIs, task leaders, and other relevant researchers must read this SOP in the light of their activities and ensure the IC approach they take is consistent with the standards laid out below. This includes **minimum criteria for information sheets and consent form templates**. It also describes clearly the kinds of activities that will require IC. The criteria following will provide requirements for ethical compliance with regulations and the expectations of the EC.

In the HBP, Information sheets and consent forms must meet the criteria set out here, be approved by the local competent ethics body, and must be submitted to Ethics Management for compliance and review procedures. Copies of specimen IC documentation will be retained by ethics management.

2. 2 Background

Directive 2001/20/EC, relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, states;

"Informed Consent is the decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation."

Although 2001/20/EC pertains to clinical practice and trials, these principles can be applied more generally.

The upcoming General Data Protection Regulation (GDPR), that will be operational across the EU, ought to be borne in mind when making consent procedures. The new Rregulation will make significant changes to the landscape of legal consent in European jurisdictions. The Information Commissioner's Office of the UK provides the following summary points:

> "•The GDPR sets a high standard for consent, but the biggest change is what this means in practice for your consent mechanisms.
>
> •The GDPR is clearer that an indication of consent must be unambiguous and

involve a clear affirmative action.

•Consent should be separate from other terms and conditions. It should not generally be a precondition of signing up to a service.

•The GDPR specifically bans pre-ticked opt-in boxes.

•It requires granular consent for distinct processing operations.

•You must keep clear records to demonstrate consent.

•The GDPR gives a specific right to withdraw consent. You need to tell people about their right to withdraw, and offer them easy ways to withdraw consent at any time.

•Public authorities, employers and other organisations in a position of power are likely to find it more difficult to get valid consent.

•You need to review existing consents and your consent mechanisms to check they meet the GDPR standard. If they do, there is no need to obtain fresh consent."[1]

The HBP will carry out research in areas that will involve data from at least (i) other research projects, (ii) data repositories, and (iii) clinical settings. There will also be other data sources, such as the HBP's own research. Some of these may pose particularly sensitive ethical challenges.

For all research involving human subjects and any use of human tissues carried out by the HBP, IC procedures have to be carried out, and ethical approval obtained, prior to commencement of the research. Where consent has been obtained for another purpose (e.g. by a BioBank or by a hospital), the ethical approval should explicitly consider whether the consent already obtained is adequate for the purpose proposed by the HBP. This pertains to 'broad consent'.

Straightforward expressions of consent to participate in research must make explicit reference to how data or samples will be obtained, used, retained and destroyed, and how procedures for informing subjects of incidental findings and for allowing withdrawal of consent will operate. Only when participants know about and agree with plans for their participation can they be said to have been sufficiently informed, and so to have given their IC.

3. 3 Stakeholders

The European Commission, other funders of the HBP, and HBP governance bodies expect all participants in the HBP to pursue a proper approach to IC. This implies that the needs of the following stakeholders should be considered:

- All HBP researchers
- Local ethics committees
- Research participants
  - Healthy volunteers
  - Patients
  - Children/Minors
  - Incompetent/Incapacitated persons
  - Vulnerable groups who risk being inappropriately coerced into participation in research (e.g. prisoners, non-EU citizens, students)

[1] Cf. https://ico.org.uk/about-the-ico/consultations/gdpr-consent-guidance/

- Physicians or other clinicians
  - In partner hospitals which curate their own data for HBP use

4. 4 Implementation

A single template covering all stakeholders' requirements is not feasible and might risk not respecting local variation in the implementation of EC directives, thereby overstepping the mark. For this reason, this proposal does not prescribe specific details, but describes a format for IC documentation. Following the EC self assessment form on the topic, it sets out what is required of such documentation. This document collects key insights about IC requirements and sets out HBP policy for informing PIs about new IC provisions as they emerge.

Materials should be locally developed to ensure that they are appropriate for specific research. Documentation of IC will require **information sheets** and **consent forms**. Directive 2001/20/EC ought to feature as the touchstone for IC templates.

Tasks involving human participants or the use of human tissues will be identified through systematic application of the Horizon 2020 ethics self-assessment exercise, which all PIs are obliged to undertake. Where consent was obtained before these SOPs came into effect, the Task leaders concerned will need to check that the IC meets their requirements. They are also responsible for ensuring that the IC is updated if IC requirements changes, or if the IC obtained does not cover the uses that the HBP will make of the data (e.g. research use of imaging data obtained for patient treatment purposes).

These and related standards will inform the decision-making of local ethics bodies. These deliberations will be helped by conscientious research design that pre-empts the conditions of standards such as the GDPR, as well as other ethics standards laid out below. Following local ethics approval, IC documents will then be reviewed by the relevant bodies in SP12. In the first instance, this will be part of the ethics compliance function of the Ethics Management team. Ethics approvals will be screened by Ethics Management prior to storing to ensure that they are adequate. The expertise of the screeners will be augmented by the more general research of the SP12 Ethics and Society sub-project. Where specific expertise is required, the EAB may also be drawn upon for advice. The screening for adequacy will be made in order to ensure ethics compliance with EC standards, and consistency across approvals to be stored for monitoring and review. PIs remain responsible for obtaining appropriate IC, but local ethics committees and broader HBP ethics-relevant bodies must check to ensure that appropriate IC forms have been used.

4.1 Outline minimal requirements

Obtaining IC involves providing research participants, or their proxies, with a written **information sheet**, describing the research and the participants' role in it, and a **consent form**, which each participant (or their proxy) must sign. As part of the ethics application process for a specific research activity, the local ethics review board which approves the research must also approve the information sheet and consent form before they are used to gather IC. Prior to signing the consent form, participants or their proxies, must also be given adequate opportunity to ask questions about the research and their participation in it. These will have to have been approved by a local body competent in assessing ethics

(e.g. university ethics committee, hospital ethics committee). Where the situation is not clear, local PIs must seek out their relevant body competent in ethics for this review. Ethics Management can assist where questions arise. For example, this may be a university ethics committee; a hospital research ethics body; a governmental office; an institutional review board, depending upon factors such as the nature of local regulatory arrangements or that of the researching institution. The body will have the task of assessing whether the forms meet the minimum criteria laid out below.

A copy of the information sheet and a blank consent form, must be forwarded to the HBP's Ethics Management team, who will maintain the database of IC materials in order to demonstrate ethics compliance. NB, The EC states that "It is enough to provide examples of the different types of forms and Information sheets you will use… (one example per type). The real forms must be kept on file and may have to be submitted later on, if requested by the Commission/Agency."

According to H2020 guidance on IC, information sheets must *minimally* contain certain information, depending upon the research activity undertaken. Building upon this guidance based on experience from HBP's Ramp Up Phase and Ethical Reviews so far, Ethics Management in conjunction with EAB representatives provide the following criteria that go beyond the generic H2020 criteria. This will ensure HBP-specific contexts are catered for. The following criteria must minimally frame HBP information sheets:

Information sheet minimal criteria
A statement that the study involves research subjects and an explanation of the purposes of the research.
The expected duration of the subject's participation.
A description of the procedures to be followed/of the medicine that is going to be tested, and an identification of any procedures which are experimental.
A statement that participation is voluntary and that consent may be withdrawn at any time and for any reason, without any negative consequences to ongoing or future treatment.
Information about who is organising and funding the research.
Details of participation, a description of any reasonably foreseeable risks, discomfort or disadvantages.
A description of any benefits to the subject or to others which may reasonably be expected from the research avoiding inappropriate expectations.
A disclosure of appropriate alternative procedures for treatment/diagnosis if any, that might be advantageous to the subject.
A statement describing the procedures adopted for ensuring data protection/confidentiality/privacy including duration of storage of personal data.
A description of how incidental findings will be handled.

A description of any planned genetic tests, including anonymity, data-handling, sensitive data policies regarding possible implications
An explanation as to whether there are any treatments or compensation if injury occurs and, if so, what they consist of, or where further information may be obtained. Insurance coverage should be mentioned.
A reference to whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a complaint or research-related injury to the subject.
A statement offering the subject the opportunity to ask questions and to withdraw at any time from the research without consequences. An explanation of what will happen with the data or samples at the end of the research period and if the data/ samples are retained or sent/sold to a third party for further research.
A reference to whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
A statement offering the subject the opportunity to ask questions and to withdraw at any time from the research without consequences.[2]
An explanation of what will happen to the *research data* at the end of the research period and whether the data are to be retained or sent/sold to a third party for further research. This should include the ability to withdraw the data up until the point of anonymisation.
An explanation of what will happen to *any samples taken during the research*, at the end of the research period and whether the samples are to be retained or sent/sold to a third party for further research. This should include the ability to withdraw the samples from any further research, up until the point of anonymisation.

Further requirements apply where research will involve **children**, where **imaging** is to be used, where **ability to assent is not present** or is impaired (i.e., all vulnerable groups). These further conditions are found in the discussion of Directive 2001/20/EC specifically for IC in H2020, to be found here. Noted in the same document is the principle that,

> "Consent should be a continuing process, especially in long-term trials or projects, researchers should foster a continuous dialogue with participants and inform them of anything new related to the trial."

The HBP is one such long-term project, and so this principle should ideally inform HBP researchers' approach. This will be reviewed periodically, at relevant stages of a given Task's progress (e.g., half way towards completion; following data collection; in advance of data source selection).

[2] This will – occasionally - raise challenges for some kinds of neuroscience research such as grids and strips placed directly on the human brain. The participant's refusal to continue must still permit the opportunity to surgically remove the grids, etc., to ensure the research participant can withdraw safely.

5. 5 Incidental findings

Depending upon the type of research project involved, a decision might need to be taken about how to deal with 'incidental findings' in the event that these arise. For this purpose, incidental findings are those arising from a study that are outside the design parameters of the study, but which may be significant for the health of participants, including their reproductive health.[3] By this definition, incidental findings can occur in research carried out on healthy volunteers, as well as on patients.

Typical examples of research studies where incidental finding might be expected to occur include (but are not limited to) genetic studies and imaging studies of the body and brain. Key decisions for researchers include whether and how incidental findings should be reported to participants or their guardians or representatives (where participants are children or non-competent adults) and whether participants' primary care doctors should also be notified (subject to participants' assent to safeguard privacy). Consideration of incidental findings will need to be addressed in the participant information sheet, as well as forming part of the IC process.[4]

Research participants might assume that researchers will identify and report any incidental findings that are discovered. This cannot be left to chance by researchers, and so the position must be made explicit. For instance, participants might choose to exercise their right **not** to know certain categories of information. Recognition of this right should be respected as part of the consent process. However, in some research contexts (or national jurisdictions) this will not be possible owing to a norm to inform (see recent German discussion, from footnote 3, p.18). This must be made clear. Unless data has been anonymized, researchers may decide to check back with a participant in the event that an incidental finding reveals a treatable life-threatening or serious condition. Efforts might be made to ascertain whether the decision **not** to be informed still applies, without revealing the actual information concerned. As a default position, wording such as the following ought to appear on consent forms:

- If incidental findings are discovered, the participant will be informed about this finding unless he/she explicitly states that he/she does not wish to be informed

or

- If incidental findings are discovered, the participant will be not informed about this finding unless he/she explicitly states that he/she does wish to be informed

or

- If incidental findings are discovered, the participant will not be informed about the findings

The strategy for dealing with suspected incidental findings will need to be considered by the ethics review body as part of the advance ethical clearance procedure.

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[3] See Wolf S, Frances P, Lawrenz, C et al., 'Managing Incidental Findings in Human Subjects Research'(2008) J Law Med Ethics 36(2): 219–211 at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2575242/

[4] Examples of different provisions drafted for different scenarios and strategies for participant information and informed consent forms are available in Appendix 3 of the Royal College of Radiologists 'Management of Incidental Findings Detected during research imaging (2011) at: https://www.rcr.ac.uk/sites/default/files/publication/BFCR(11)8_ethics.pdf

6. 6 IC procedure overview

This is a graphical representation of how IC procedures generally ought to feature in the flow of research design.

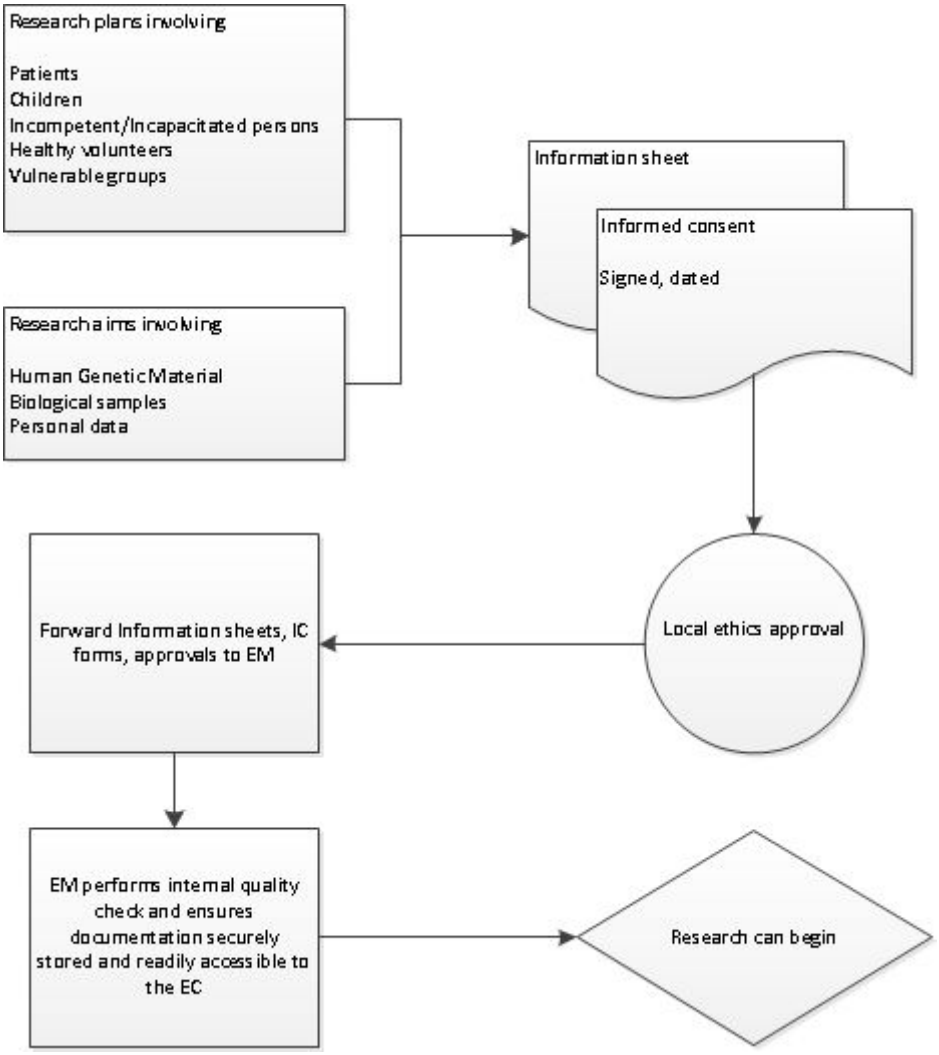

Figure 1: Graphical representation of procedures for informed consent

7. 7 Evaluation of IC materials

Adequacy of IC materials must be assessed at the local level, by the local competent body. As a matter of course, these materials must contain at least the minimum criteria set out above. Where children, imaging or vulnerable groups are involved, further information must be provided (See section 4.1.)

Drawing upon FP7's Guidance For Applicants: Informed Consent, a statement on IC as 'a continuing dialogue'[5] - a benchmark for IC in large projects from the perspective of the EC - would be highly desirable where possible by the time that half of the planned research duration has passed. Practically, midway through the Task, a document would be prepared

[5] Cf. http://ec.europa.eu/research/participants/data/ref/fp7/89807/informed-consent_en.pdf specifically

that demonstrates how HBP researchers have implemented IC in terms of how participants have been kept informed of developments in the research. This might be via participant contact, or by more general means such as public reporting of research activities, outcomes, and societal relevance. The document should include references to any incidental findings issues, should they have arisen. Where IC as a dialogue is not implemented, a statement on why this is not possible, or not practicable ought to be forthcoming. This statement will be reviewed and retained by the HBP Ethics Management. This would represent best practice, and if possible it ought to be pursued.

7.1 Metrics

The following are key dimensions that will structure assessment of IC provisions for research.

- Local ethics approval is present
- *At least* minimal requirements for information sheet are met
- Further details present where necessary
- 'IC as an ongoing dialogue' statement

7.2 Schedule

IC must be in place before research gets underway. To reflect the possibility of changing methods, and evolving practices, PIs will be asked to confirm IC adequacy periodically after research is underway.

8. 8 IC compliance actions timeline

The European Commission can request the HBP to provide it with full IC documentation for any part of HBP research at any time. HBP Ethics Management will thus ensure that the project's IC documentation is systematically gathered, archived and readily accessible to the EC.

Time	Stage	Responsible
Prior to research	Information sheets, IC templates prepared according to research aims and protocols, and submitted to local ethics body	PIs
	Information sheets and IC templates approved	Local ethics body
	Approved information sheets and IC templates sent to HBP Ethics Management for filing	PIs
	Information sheets and IC forms presented to relevant parties (e.g. research participants, legal guardians, data controllers)	PIs
As research gets	Archive IC templates/forms	PIs,

underway		Ethics Management
Before halfway through research period	Request update from PIs	Ethics Management
	Assess quality of 'IC as a dialogue', or of explanation of its absence.	HBP Ethics Management, PIs, Task leaders

9. 9 IC SOP Development timeline

This discussion has concerned all the relevant issues that constitute the SOP on IC. The structure of the consultation for the SOP's development is as follows:

Stage	**Time**
Submission of IC SOP deliverable mandated by ethics review	M5
Development of draft SOP for circulation	M6
Circulation of draft SOP among relevant SPs (e.g. SP2, SP3, SP8) and EAB (including Webinar meeting)	M7-8
Consultation for collecting feedback	M9
Webinar on IC[6]	M10
Re-circulation of SOP following edits	M10
SOP finalisation	M12

[6] https://www.humanbrainproject.eu/en_GB/-/first-hbp-stakeholder-webinar-series?redirect=https%3A%2F%2Fwww.humanbrainproject.eu%2Fen_GB%2Fnews-list%3Fp_p_id%3D101_INSTANCE_qvWAPKvcO4xA%26p_p_lifecycle%3D0%26p_p_state%3Dnormal%26p_p_mode%3Dview%26p_p_col_id%3Dcolumn-2%26p_p_col_count%3D1