D8.01 Point of contact/advisors

116026 – HARMONY

Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in Hematology

WP8 – Legal, Ethics and Governance

Lead contributor	Klaus Wassermann, Medical University of Vienna (9 – MUW)
	klaus.wassermann@meduniwien.ac.at
Other contributors	Christiane Druml, Medical University of Vienna (9 – MUW)
	Janet Addison, Amgen (47 – AMGEN)
	John Edward Butler-Ransohoff, Bayer (49 – BAYER)

Due date	28 February 2017
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Deliverable type	R
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Description of Action	**Version**	**Date**
	V3.0 (nr 3)	29 November 2016

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Document History

Version	Date	Description
V1.0	15 March 2017	Initial Draft by WP8
V1.1	03 April 2017	Revision by the PMO/Charo Penadés
V1.2	14 April 2017	Re-drafting by WP8
V1.3	20 April 2017	Submission to HARMONY's Executive Committee (EC) for review
V1.4	04 May 2017	EC review comments included by WP8
V1.5	15 May2017	SC review and comments by Janssen/C. Donatti
V1.6	29 May 2017	Re-drafting by WP8 in reply to Janssen's/C. Donatti's comments
V1.7	28 June 2017	Content adjustment after EAB meeting
V1.8	07 July 2017	Re-drafting by WP8 in reply to the EC's updates in V1.7
V1.9	13 December 2017	Re-drafting and updating by WP8 after additional comments by the EC

List of Acronyms/Definitions

Acronym	Description
AML	Acute Myeloid Leukemia
AMLSG	Acute Myeloid Leukemia Study Group (German-Austrian consortium)
BD4BO	The IMI Big Data For Better Outcomes initiative
CSA DO-IT	IMI Coordination and Support Action "DO-IT" (BD4BO)
DPD	Data Protection Directive
EAB	HARMONY's external Ethics Advisory Board
EAP	HARMONY's Expert Advisory Panel
ELF	External law Firm
GDPR	General Data Protection Regulation
HARMONY	Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in Hematology (the IMI project this deliverable document is part of)
HM	Hematologic Malignancy
ICF	Informed Consent Form
IMI	Innovative Medicines Initiative
MUW	Medical University of Vienna (Austria)
PMO	HARMONY's Project Management Office
UNIVIE	University of Vienna
UULM	University of Ulm (Germany)
WP	Work Package
WPL	Work Package Leader

D8.01 POINT OF CONTACT/ADVISORS

1. PUBLISHABLE SUMMARY

Establishing a point of contact and infrastructure

A project manager (Klaus Wassermann, MUW) was employed as of 01 January 2017 to coordinate all activities of WP8. A point-of-contact infrastructure for WP8 was appropriately implemented at the Medical University of Vienna and was fully operational by 09 January 2017.

Proposing members of HARMONY's external Ethics Advisory Board (EAB)

Upon a request by IMI for establishing an external advisory body in the field of ethics, three international ethics experts were nominated to form HARMONY's Ethics Advisory Board (EAB) by 09 January 2017. All three experts agreed to serve on the EAB. Developing and signing of formal documents to agree the terms of collaboration with the EAB members is currently in progress.

Establishing legal and ethics advisory networks within HARMONY

European data protection legislation is a complex topic involving not only EU law, but also legislation in individual member states. To efficiently deal with this complexity, legal counsel from within the WP8 co-lead EFPIA companies (BAYER, AMGEN), who are collaborators on the project, has been identified. In addition, work is ongoing to extend the network of EFPIA legal advisors and to form a network of representatives from local ethics committees, respectively.

Setting up the "Proof-of-Principle" study (D8.03)

A test case, known internally as the Proof-of-Principle Study (HARMONY deliverable D8.03, together with WPs 2, 3, 4, 5 and 6) or pilot study, has been conceived to identify any procedural and technical, but also legal and ethical issues that may arise during the implementation of HARMONY's data analysis platform. To enable setting up the pilot study efficiently a list of legally and ethically relevant issues has been identified and discussed among members of WP8 and among relevant and interested representatives of other HARMONY work packages (WP1, WP2, WP3, WP4, WP6) as well as extensive consultations of external advisors.

A De-Facto-Anonymisation approach has been jointly developed which is conceived to provide a data handling procedure being both compliant with data protection regulation and practical in terms of providing HARMONY with a feasible means to achieve its goals. A renowned law firm was commissioned by the HARMONY consortium to provide a formal green-light expertise on the De-Facto-Anonymisation approach, permitting HARMONY to officially launch the Proof-of-Principle Study in early 2018.

For detailed information on the individual items mentioned above please refer to Chapter 4 of this document, titled "Accomplishments within D8.01".

2. SCOPE

HARMONY is a European Network of Excellence within the IMI public-private partnership initiative which intends to shed light on the molecular basis, development and outcomes of hematologic malignancies (HM). The project's WP8 deals with legal, ethical and compliance issues which are critical for HARMONY's successful implementation in accordance with prevailing laws and norms as regards aspects of data privacy, data reuse and data repurposing as these pertain to HARMONY research projects. This deliverable document (D8.01) presents the tasks that have been completed within WP8's task 8.1 titled Ethical and Legal Support.

3. PURPOSE AND OBJECTIVES

The tasks described in this deliverable document are of core relevance for implementing HARMONY's Proof-of-Principle study, which is being implemented in close collaboration with HARMONY's WP2, WP3 and WP4 in particular, all of which are involved in handling HM data from previously conducted studies within the context of acute myeloid leukemia (AML).

4. ACCOMPLISHMENTS WITHIN D8.01

4.1. Point of contact and infrastructure

An IMI-experienced project manager was employed by WP8 leader Medical University of Vienna as of 1 January 2017. A point-of-contact infrastructure for WP8 was implemented at the MUW and was fully operational by 09 January 2017.

Full contact details of the HARMONY WP8 project manager operating as the WP8 point of contact:

Klaus Wassermann
Josephinum - Ethics, Collections and History of Medicine
Medical University of Vienna
Währingerstrasse 25
1090 Vienna, Austria
Tel: +43/ 1 / 40160 / 26002
Fax: +43/ 1 / 40160/ 9 26000
klaus.wasserman@meduniwien.ac.at

4.2. Formation of the external Ethics Advisory Board (EAB)

In the preparatory phase of the HARMONY project's launch IMI requested of HARMONY to establish an independent Ethics Advisory Board (EAB). This board's task was to be advising on ethical topics during the project's running period, particularly providing approval of HARMONY's project reporting. Thus, three renowned international experts were nominated by WP8 leader Christiane Druml (MUW) to form HARMONY's Ethics Advisory Board (EAB) by 09 January 2017.

The EAB member's full contact details:

Prof. Inez de Beaufort
Professor of Medical Ethics
PO Box 2040
3000 CA Rotterdam, The Netherlands
Tel: +31 (0)10 7044145
Fax: +31 (0)10 7044735
www.erasmusmc.nl/ethiek
i.debeaufort@erasmusmc.nl

Prof. Federico de Montalvo Jääskeläinen
Profesor propio adjunto Derecho Constitucional
Director Máster Universitario en Acceso a la Abogacía Facultad de Derecho
C/ Alberto Aguilera 23
28015 Madrid, Spain
Tel: +34 91 542 28 00/2184
fmontalvo@comillas.edu
http://www.comillas.edu

Prof. Peter Bauer
Professor Emeritus
Institut für Medizinische Statistik
Medical University of Vienna
Spitalgasse 23
1090 Vienna, Austria
Tel: +43-1- 40400 / 74950
Fax: +43-1- 40400 / 74770
peter.bauer@meduniwien.ac.at
http://cemsiis.meduniwien.ac.at/en/

A formal agreement document for collaboration between HARMONY and the members of the EAB has been drafted by WP8 and sent to HARMONY's PMO on 9 March 2017. The full text of the draft Memorandum of Understanding document defining the form of collaboration between members of the EAB and HARMONY is included in Annex 1 of this document.

HARMONY's WP1/PMO has established the project's coordination with the EAB.

4.3. Legal and ethics advisory networks within HARMONY

Initial contacts to legal advisors from within the participating EFPIA companies have been established. Any HARMONY-related activity of legal advisors of WP8 EFPIA partners Bayer and AMGEN will be reported as in-kind contributions by the respective company.

Legal advisor for HARMONY at Bayer (Berlin, Germany):

Dr. Fabian Dorra
Legal Counsel
Rechtsanwalt (Syndikusrechtsanwalt)
Bayer Aktiengesellschaft
Law, Patents & Compliance - Pharmaceuticals
Building S101 / 15th Floor, Room 212
Müllerstrasse 178
13353 Berlin, Germany
Tel: +49 30 468 194736
Fax: +49 30 468 14086
E-mail: fabian.dorra@bayer.com

Legal advisor for HARMONY at Amgen (Zug, Switzerland):

Kathleen Fadden
Senior Legal Counsel
Amgen (Europe) GmbH
Dammstrasse 23
6301 Zug, Switzerland
Tel: +41 413692 554
E-mail: kfadden@amgen.com

Legal advisor for HARMONY at Menarini (Florence, Italy):

Davide Ajello
Compliance specialist
Direzione Corporate Antitrust e Privacy Compliance
A. Menarini IFR
Via Dei Sette Santi 1/3
50131 Florence, Italy
Tel. +39 055 56809617
E-mail: dajello@menarini.it

Contact details of persons active in the ethics field have been collected from within the project partner institutions:

Dr. María Belén Vidriales Vicente
Servicio de Hematología
Complejo Asistencial
Universitario de Salamanca
Paseo de San Vicente, 58-182
37007 Salamanca, Spain
Tel: +34 923291384
Fax: +34 923294624
E-mail: mbvidri@usal.es

Prof. Ghislaine van Thiel
Julius Center, Medical Humanities Research
University Medical Center Utrecht
PO Box 85500
3508 GA Utrecht, The Netherlands
Tel: +31 88 75 513 49
Mob: +31 6 2369 85 90
E-mail: G.J.M.W.vanThiel@umcutrecht.nl

Irene Schlünder
Bioethics and International Relations
BBMRI and TMF
TMF – Technologie- und Methodenplattform für die vernetzte medizinische Forschung e.V.
Charlottenstraße 42
10117 Berlin, Germany
Tel: +49 30 22 00 24 743
E-mail: Irene.Schluender@tmf-ev.de

WP8 representatives are working on extending these legal and ethics advisory networks by initiating personal contacts via e-mail, telephone calls and in face-to-face meetings.

4.4. Coordination of synergies within all IMI BD4BO initiatives

The IMI BD4BO initiative's projects are all facing similar challenges regarding compliance with legal and ethical requirements. Therefore, IMI has created the Coordination and Support Action DO-IT (CSA DO-IT, launched on 01 February 2017) to tackle these issues in a combined synergistic fashion. HARMONY WP8 representative John Edward Butler-Ransohoff (Bayer) has been involved in this CSA activity from the start. Since mid-2017 Klaus Wassermann (MUW) has been actively involved in the CSA DO-IT's activities, attending teleconferences and giving presentations at meetings.

HARMONY's WP8 is continuing to assess the work to be undertaken by CSA DO-IT to understand the contributions and benefits for HARMONY and to cooperate in developing sustainable data handling solutions all IMI BD4BO projects will require.

4.5. Setting up the "Proof-of-Principle" study (D8.03)

To enable proceeding with setting up the Proof-of-Principle study (D8.03) efficiently, legally and ethically relevant issues have been identified and discussed among members of WP8, among relevant representatives of different HARMONY work packages (WP1, WP2, WP3, WP4, WP6, WP8) and by consulting external advisors.

In particular, to clarify and resolve the practicalities associated with implementing the Proof-of Principle study, WP8 has called a number of Meetings in Vienna:

1. **WP8 preparatory meeting to HARMONY's first General Assembly (12 January 2017)**

   Participants:

   - Janet Addison (Amgen, WP8)
   - John Edward Butler-Ransohoff (Bayer, WP8)
   - Fabian Dorra (Bayer, WP8)
   - Christiane Druml (MUW, WP8)
   - Klaus Wassermann (MUW, WP8)

   Minutes on SharePoint:
   https://synapsemanagers.sharepoint.com/:b:/r/sites/harmony/wp8/Shared%20Documents/WP8%20Meetings/20170221_2nd_VIENNA_MEETING_OF_WP8.pdf?csf=1

2. **Inter-WP meeting on HARMONY's data structure and handling (21 February 2017)**

   Participants:

   - Janet Addison (Amgen, WP8)
   - Peter Bauer (MUW, advisory participant)
   - Lars Bullinger (UULM, WP2)
   - John Edward Butler-Ransohoff (Bayer, WP8)
   - Fabian Dorra (Bayer, WP8)
   - Christiane Druml (MUW, WP8)
   - Rafael Navajo (GMV, WP3)
   - Renate Schulze-Rath (Bayer, WP2)
   - Michel Van Speybroeck (Janssen, WP3)
   - Klaus Wassermann (MUW, WP8)
   - Christiane Wendehorst (UNIVIE, advisory participant)

Minutes in ANNEX 2 of this document and on SharePoint:
https://synapsemanagers.sharepoint.com/:b:/r/sites/harmony/wp8/Shared%20Documents/WP8%20Meetings/20170221_Minutes_WP8_data_issues_Vienna.pdf

3. **Inter-WP working meeting on legal and ethical framework (16 May 2017)**

Participants:

- Janet Addison (Amgen, WP8)
- Pamela Bacon (Celgene, WP1)
- John Edward Butler-Ransohoff (Bayer, WP8)
- Fabian Dorra (Bayer, WP8)
- Christiane Druml (MUW, WP8)
- Kathleen Fadden (Amgen, WP8)
- Uriel Landesmann (MUW, advisory participant)
- Rafael Navajo (GMV, WP3)
- Irene Schlünder (TMF, BBMRI, CSA DO-IT advisory participant)
- Klaus Wassermann (MUW, WP8)

Minutes on SharePoint:
https://synapsemanagers.sharepoint.com/:b:/r/sites/harmony/wp8/Shared%20Documents/WP8%20Meetings/20170516_minutes_WP8_Do-IT_ICF_Vienna.pdf?csf=1

4. **Meeting of the Ethics Advisory Board (EAB) (19-20 June 2017)**

Participants:

- Peter Bauer (MUW, EAB)
- Inez de Beaufort (Erasmus MC Rotterdam, EAB)
- Lars Bullinger (UULM, WP2)
- John Edward Butler-Ransohoff (Bayer, WP8)
- Christiane Druml (MUW, WP8)
- Jesus Maria Hernandez Rivas (IBSAL, WP1)
- Federico de Montalvo Jääskeläinen (Universidad Pontifica Comillas, EAB)
- Rafael Navajo (GMV, WP3)
- Klaus Wassermann (MUW, WP8)

Minutes in ANNEX 3 of this document and on SharePoint:
https://synapsemanagers.sharepoint.com/:b:/r/sites/harmony/wp8/Shared%20Documents/WP8%20Meetings/20170619-20_Minutes_WP8_data_EAB_Vienna.pdf?csf=1

5. **WP8 exchange meeting with Ethics WPL of IMI BigData@Heart (9 July 2017)**

Participants:

- John Edward Butler-Ransohoff (Bayer, WP8)
- Christiane Druml (MUW, WP8)

- Ghislaine van Thiel (Utrecht University, WPL BigData@Heart)
- Klaus Wassermann (MUW, WP8)

6. **Inter-WP meeting on data handling techniques and compliance (18 October 2017)**

   Participants:

   - Tamás Bereczky (Leukanet, WP6)
   - John Edward Butler-Ransohoff (Bayer, WP8)
   - Patricia van Dijk (Novartis, WP1)
   - Francesco Cerisoli (EHA, WP7)
   - Christina Donatti (Janssen, WP3/4)
   - Christiane Druml (MUW, WP8)
   - Enrico Gampieri (UNIBO, WP5)
   - Flemming Moos (Osborne Clarke, ELF)
   - Santiago Moralejo (IBSAL, WP1)
   - Guillermo Sanz (HULAFE, WP1)
   - Ruben Villoria (GMV, WP3/4)
   - Klaus Wassermann (MUW, WP8)

   Minutes in ANNEX 5 of this document and on SharePoint:
   https://synapsemanagers.sharepoint.com/:b:/r/sites/harmony/wp8/Shared%20Documents/WP8%20Meetings/20171018_Minutes_Inter-WP_Vienna_final.pdf?csf=1

4.6. Guidance based on research and expert discussions

4.6.1. Status of 7 July 2017 (intermediary)

Although this status summary of discussions and conclusions is obsolete as of 13 December 2017 in terms of detailed guidance on HARMONY's data processing given by WP8, the section has been left in this deliverable document as a reference to the work that has gone into solving these issues.

- For a full-scale implementation, later on the pilot study ideally needs to be fully scalable. If possible, no compromises shall be made in favour of short-term solutions regarding data selection and handling which would not address the issues of the longer-term perspective.
- Using pseudonymised data within HARMONY is the most desirable option, (in absence of patient consent for reuse of data).
- Have existing informed consent forms (ICFs) for pilot study data checked by a specialised legal counsel who has broad experience with the jurisdiction in the field is essential in order to assess whether the consent covers the remit of each research project.
- Develop a HARMONY-compatible ICF and have it evaluated by a specialised legal counsel who knows the jurisdiction in the field
- Test pilot with generated random data if necessary.

- Fully anonymise/use fully anonymised data only if there is no other possibility to proceed with the pilot study.
- The data protection legal aspects in terms of balancing the public interest and individual privacy rights were discussed. It was taken for granted that the sharing of individual patient information for the purposes of data analysis in the frame of HARMONY will have many benefits for patients. The question is how to do so in a way that protects individual privacy while ensuring that the data is of sufficient quality that the analysis will yield useful and meaningful results.
- A proper anonymisation (better de-identification) procedure must be both reasonable and defensible, i.e.: de-identification that meets current standards and can therefore be presented to legal authorities as evidence that HARMONY has taken its legal and ethical responsibility towards patients seriously. On the one hand, the benefits of the project for the health of the community should be considered; on the other hand, also the risks for the personal privacy should be considered, to balance both interests, which could be fulfilled through a de-identification method where personal data can be protected without a complete anonymisation.
- Lars Bullinger and Rafael Navajo will describe their strategy in a document which will be submitted to an external law firm to be reviewed and legally evaluated. This needs to be done as soon as possible.

The informed consent given by data subjects for generating the AMLSG data likely does not allow for secondary use of this data in a straightforward manner. WP8's thus advises fully anonymising data from the AMLSG for use within the HARMONY Proof-of-Principle Study.

For more information please refer to Annex 3 which lists the complete minutes of the WP8 and EAB meeting in Vienna on 19/20 June 2017.

4.6.2. Status of 13 December 2017 (current)

The initial WP8 guidance on HARMONY's data handling for the HARMONY Proof-of-Principle Study led to further extensive discussions among HARMONY's Executive Committee (EC) and other work packages, HARMONY's external Ethics Advisory Board (EAB), sister IMI BD4BO projects, the IMI CSA DO-IT initiative and, not least, within HARMONY's WP8 itself. In essence, these discussions concluded that it was not feasible to sensu-stricto-anonymise data as project's core goals (e.g., tracing disease progression, updating and extending data records) as well as compliance with current and future legislation (e.g., data subjects' right to data deletion, right to amend data, right to data portability) would be put in jeopardy.

In order to be able to launch the Proof-of-Principle Study in 2017 or early 2018, HARMONY needs to comply with the legal framework of the EU Data Protection Directive (Directive 95/46/EC) which will be superseded by the EU General Data Protection Regulation (EU) 2016/679 on 25 May 2018. To address all of HARMONY's data protection issues effectively, WP8, together with all advisory bodies mentioned

above, developed an approach to De-Facto-Anonymisation, the essence of which is presented in ANNEX 7 of this document.

To proceed further efficiently with implementing the proposed De-Facto-Anonymisation techniques the HARMONY consortium decided to appoint an external law firm (ELF) to provide a legal expertise regarding the compliance of the proposed De-Facto-Anonymisation approach on the basis of the EU DPD. A selection procedure was set up by industry coordinator Patricia van Dijk on behalf of HARMONY's EFPIA partner Novartis. From a list of six applicants Osborne Clarke was chosen to be commissioned.

HARMONY's contact at Osborne Clarke:

Dr. Flemming Moos
Fachanwalt für Informationstechnologierecht
Osborne Clarke
Reeperbahn 1
20359 Hamburg
E-mail: flemming.moos@osborneclarke.com
Tel: +49 40 55436 4052 (direct)
Tel: +49 40 55436 4060 (Assistant)
Mobile: +49 172 249 59 01
www.osborneclarke.com

Following his participation in the inter-WP meeting in Vienna on 18 October 2017 Dr. Moos provided HARMONY with a draft document resulting in a favourable opinion on the use of the De-Facto-Anonymisation technique. The most recent version of this document's executive summary, which was also provided to HARMONY's Steering Committee on 5 December 2017, is attached here in ANNEX 8.

ANNEX 1: EAB's Advisory Agreement
(Status: 11th April 2017)

ADVISORY AGREEMENT

THIS AGREEMENT is made and entered force as of the xx of April, 2017 between the HARMONY Consortium Members (the "**Consortium**") represented by **Dr Jesús María Hernández Rivas**, as Project Coordinator on behalf of Consortium and as their duly authorized representative per the mandate stated in clause 11.5 of the Consortium Agreement, and *[Name of consultant]* ("**Advisor**").

WHEREAS,

The Consortium has been formed under the Innovative Medicines Initiative 2 ("**IMI2**") for establishing the project called "Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in Haematology: HARMONY" (Grant Agreement No. 116026).

Subject to the Consortium Agreement, an ***Ethics Advisory Board***[1] is established to provide impartial and non-binding advice as decision-making support on specific ethical, regulatory and data sharing issues raised under the auspices of the HARMONY project.

The Advisor has the requisite expertise in the field and is willing to serve as a member of the HARMONY Consortium ***Ethics Advisory Board.***

Therefore, the Consortium and the Advisor desire to enter this

AGREEMENT:

1. ENGAGEMENT OF SERVICES AND COMPENSATION

1.1 The Consortium hereby appoints Advisor as a member of the Ethics Advisory Board. Advisor, pursuant the provisions of this Agreement. Advisor agrees to serve a member of the Ethics Advisory Board in accordance with the HARMONY Consortium Agreement.

1.2 . Such **Services** will include:

- Review and monitor the observation and the proper application of the ethical rules by the Beneficiaries to be adapted on a case-by-case basis;
- Provide expert interpretation, analysis and recommendations to the Beneficiaries, the General Assembly, and the Executive Committee on operational aspects of data sharing; "secondary use" of data; the use of anonymization and de-identification strategies; and how protection of personal data will be assured in the course of HARMONY implementation;

[1] Understanding "Ethics Advisory Board" as defined in the guidance document "The Roles and Functions of Ethics Advisors/Ethics Advisory Boards in EC funded Projects", European Commission, DG Research and Innovation, December 2012, http://ec.europa.eu/research/participants/data/ref/h2020/other/hi/ethics-guide-advisors_en.pdf.

- Provide advice on the compliance with European ethical laws and regulation and with different ethics guidelines, laws, and regulations of countries where studies are being performed;
- Review documents, operational procedures, and reports for their compliance with ethical standards upon request of the Executive Committee, the Steering Committee or WP8 Leadership;
- Be available to meet upon request of the General Assembly or Executive Committee, but at least once every twelve (12) months during the HARMONY implementation; and
- Submit a report on ethics compliance to the IMI with the HARMONY Periodic Reports.

1.3 The parties agree that the Advisor shall not be compensated for the performance of the Services. However, the Consortium will pay for reasonable travel expenses and hospitality, such as flights (business class airfare for intercontinental flights and economy class airfare for intracontinental flights), train travel, accommodation (up to 4-star rating), work related meals, and transportation. In addition, Advisor shall be reimbursed for other reasonable travel expenses incurred by Advisor in connection with providing the Services, subject to the receipt of invoices or receipts. Any payments will be made by the Project Coordinator within 90 days upon receipt of a correct invoice containing the original receipts.

2. NON-DISCLOSURE

2.1 Advisor agrees not to reproduce any information regarding the Action and all results of the cooperation with the Consortium in any format, except as necessary for Advisor's performance of Services. Advisor will keep in confidence and trust such information or results and shall not use or disclose such information to any third party without a prior written consent of the Consortium, unless such actions are required in the ordinary course of performing Services for the Consortium pursuant to this Agreement. This confidentiality and non-use obligation shall remain in effect for ten (10) years after the Consortium Agreement expires or is terminated.

3. TERM

3.1 Unless previously terminated as set forth below, this Agreement comes into force upon signature by the parties and continues effective until the effective date of termination of the HARMONY Project (31st of December, 2021).

3.2 Either party shall terminate this Agreement at will upon thirty (30) days written notice to the other.

4. MISCELLANEOUS

4.1 Advisor agrees to comply with all applicable laws and regulations in the performance of the Services pursuant to this Agreement.

4.2 Advisor shall not have the authority to act on behalf of the Consortium or to obligate the Consortium by contract or otherwise.

4.3 This Agreement contains the entire agreement between the Advisor and the HARMONY Consortium. Any amendments to this Agreement shall be made in writing.

4.4 This Agreement shall be construed, controlled and interpreted by the laws of Belgium, regardless of its conflict of laws provisions. Exclusive place of jurisdiction shall be Brussels.

IN WITNESS WHEREOF,

the parties hereto have caused this Agreement to be executed in two duplicates.

Consortium	***[Advisor]***
Name: **Jesús María Hernández Rivas**	Name:
Function: **Project Coordinator**	Function:
Place:	Place:
Date:	Date:

Prof Emeritus Peter Bauer
Medical University of Vienna
Spitalgasse 23, 1090 Wien, Austria

11th April 2017

HARMONY Ethics Advisory Board – Letter of Invitation

Dear Prof Bauer,

On behalf of the HARMONY Executive Committee, I am pleased to invite you to become a member of the HARMONY Ethics Advisory Board.

The HARMONY Alliance is an European Network of Excellence in haematology, funded through the Innovative Medicines Initiative (IMI), a public-private partnership between the European Commission and the European Federation of Pharmaceutical Industry Associations (EFPIA) dedicated to health related R&D. HARMONY comprises key stakeholders in the clinical, academic, patient advocacy, HTA, regulatory, information technology and pharmaceutical fields, who have joined forces to break down information silos and unlock valuable knowledge across multiple Hematologic Malignancies using Big Data techniques. HARMONY covers multiple myeloma (MM); acute myeloid leukemia (AML); acute lymphoblastic leukemia (ALL); chronic lymphocytic leukemia (CLL); non-Hodgkins lymphoma (NHL); myelodysplastic syndromes (MDS); and paediatric hematologic malignancies. HARMONY is funded for 5 years and activities and tasks will be accomplished within that period.

We believe that independent external ethics advice is crucial for our success. We also credit your expertise, knowledge, and professional track-record as a valuable decision-making support to HARMONY on the compliance with European ethical laws and regulations, the operational aspects of data sharing, the secondary use of data, and the use of anonymization strategies. Hence, we would like to formally invite you hereby to be a member of the HARMONY Ethics Advisory Board.

The Board shall meet once a year in October, in concurrence with HARMONY's General Assembly and we will reimburse you for your travel expenses. We may also have some questions or discussion throughout the year by email or videoconference. Because of the confidential nature of some of the matters to be discussed, Advisors are requested to first sign an Advisory Agreement, which we enclose for your perusal.

Thank you for taking the time to consider being a part of the HARMONY Ethics Board and kindly let us know your decision, which we hope positive, no later than 28th April.

I will follow up this invitation with a phone call to discuss any question you may have. In the meantime, you can reach me by phone at +34 626 308549 or by email at jmhr@usal.es.

Sincerely,

Prof Dr Jesús María Hernández Rivas
HARMONY Coordinator

Prof Inez de Beaufort
Erasmus Medical Center University of Rotterdam
's-Gravendijkwal 230. 3015 CE Rotterdam, The Netherlands

11th April 2017

HARMONY Ethics Advisory Board – Letter of Invitation

Dear Prof de Beaufort,

On behalf of the HARMONY Executive Committee, I am pleased to invite you to become a member of the HARMONY Ethics Advisory Board.

The HARMONY Alliance is an European Network of Excellence in haematology, funded through the Innovative Medicines Initiative (IMI), a public-private partnership between the European Commission and the European Federation of Pharmaceutical Industry Associations (EFPIA) dedicated to health related R&D. HARMONY comprises key stakeholders in the clinical, academic, patient advocacy, HTA, regulatory, information technology and pharmaceutical fields, who have joined forces to break down information silos and unlock valuable knowledge across multiple Hematologic Malignancies using Big Data techniques. HARMONY covers multiple myeloma (MM); acute myeloid leukemia (AML); acute lymphoblastic leukemia (ALL); chronic lymphocytic leukemia (CLL); non-Hodgkins lymphoma (NHL); myelodysplastic syndromes (MDS); and paediatric hematologic malignancies. HARMONY is funded for 5 years and activities and tasks will be accomplished within that period.

We believe that independent external ethics advice is crucial for our success. We also credit your expertise, knowledge, and professional track-record as a valuable decision-making support to HARMONY on the compliance with European ethical laws and regulations, the operational aspects of data sharing, the secondary use of data, and the use of anonymization strategies. Hence, we would like to formally invite you hereby to be a member of the HARMONY Ethics Advisory Board.

The Board shall meet once a year in October, in concurrence with HARMONY's General Assembly and we will reimburse you for your travel expenses. We may also have some questions or discussion throughout the year by email or videoconference. Because of the confidential nature of some of the matters to be discussed, Advisors are requested to first sign an Advisory Agreement, which we enclose for your perusal.

Thank you for taking the time to consider being a part of the HARMONY Ethics Board and kindly let us know your decision, which we hope positive, no later than 28th April.

I will follow up this invitation with a phone call to discuss any question you may have. In the meantime, you can reach me by phone at +34 626 308549 or by email at jmhr@usal.es.

Sincerely,

Prof Dr Jesús María Hernández Rivas
HARMONY Coordinator

Prof Federico de Montalvo Jääskeläinen
Universidad Pontificia Comillas ICAI-ICADE
Calle de Alberto Aguilera, 23. 28015 Madrid, Spain

11th April 2017

HARMONY Ethics Advisory Board – Letter of Invitation

Dear Prof de Montalvo Jääskeläinen,

On behalf of the HARMONY Executive Committee, I am pleased to invite you to become a member of the HARMONY Ethics Advisory Board.

The HARMONY Alliance is an European Network of Excellence in haematology, funded through the Innovative Medicines Initiative (IMI), a public-private partnership between the European Commission and the European Federation of Pharmaceutical Industry Associations (EFPIA) dedicated to health related R&D. HARMONY comprises key stakeholders in the clinical, academic, patient advocacy, HTA, regulatory, information technology and pharmaceutical fields, who have joined forces to break down information silos and unlock valuable knowledge across multiple Hematologic Malignancies using Big Data techniques. HARMONY covers multiple myeloma (MM); acute myeloid leukemia (AML); acute lymphoblastic leukemia (ALL); chronic lymphocytic leukemia (CLL); non-Hodgkins lymphoma (NHL); myelodysplastic syndromes (MDS); and paediatric hematologic malignancies. HARMONY is funded for 5 years and activities and tasks will be accomplished within that period.

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I will follow up this invitation with a phone call to discuss any question you may have. In the meantime, you can reach me by phone at +34 626 308549 or by email at jmhr@usal.es.

Sincerely,

Prof Dr Jesús María Hernández Rivas
HARMONY Coordinator

ANNEX 2: Outcomes of the inter-WP face-to-face meeting in Vienna, 21 February 2017

WP2 participants:

- Lars Bullinger (LB)
- Renate Schulze-Rath (RS)

WP3 participants:

- Rafael Navajo (RN)
- Michel Van Speybroeck (MV), via teleconference line

WP8 Participants:

- Janet Addison (JA)
- John Edward Butler-Ransohoff (JB)
- Fabian Dorra (FD)
- Christiane Druml (CD, chair)
- Klaus Wassermann (KW, minutes)

External/guest participants:

- Peter Bauer (PB)
- Christiane Wendehorst (CW)

Main Discussion Points

Pseudonymisation, not anonymisation

Anonymising data (in the strict legal sense) for use within HARMONY will take harmony's data handling procedures completely out of data protection legislation (FD). However, anonymising data also will compromise the research data itself, bearing a considerable risk of blurring feeble biomedical data, rendering it useless for proper research purposes (PB).

It was agreed that, from a technical perspective, using pseudonymised data (in the strict legal sense) within HARMONY for the pilot study (and beyond) is the most desirable option. A pseudonymisation paradigm will require a third-party encoding solution (FD). A highly protected infrastructure for data storage needs to be developed in parallel (LB).

Obviously, there is no common understanding concerning the term "anonymisation" which seems to be confused with "pseudonymisation". Anonymised data are data which can never be traced back to the person of origin and thus is "historic" data which can't be updated later. Otherwise, the term "anonymisation" will not be legally applicable.

Ethical aspects

There is a certain risk of conflict of interest, i.e., HARMONY members requesting as well as approving data usage and analysis. An ethics committee (EAB?) needs to approve of any research question submitted to HARMONY. Alternatively, the project's Experts Advisory Panel (EAP) could be requested to formally approve of every research question submitted from a scientific point of view (CD).

For ethical approval regarding secondary use of EFPIA partners' data it is stated that EFPIA companies will need to refer back to the respective ethics committees where the study has been conducted (JA).

"Fake" data for initial testing ("to make the platform great again")

Given the current time pressure within the project, randomly generated data might be used for initial testing of the pilot implementation. The criterion for success will be identical analysis results in two consecutive data analysis runs (PB). This is common practice in complex data analytics (MV).

Updating individual's data sets

HARMONY demands a data solution which enables updating individual's data sets with more recent data, or extending data records (FD). This is not possible if the data is anonymised (in the strict legal sense). Here as well, a pseudonymisation approach will be the only way to follow to maintain all necessary data handling options.

Arranging for individual patients to give a full HARMONY-compatible informed consent retrospectively is hardly feasible and will not be pursued (PB, JB). There will also be the risk of bias towards patients who have survived since respective studies were conducted (CD).

Managing Risk of Financial Penalties

If HARMONY decides to adopt a general pseudonymisation policy for data handling, violating data protection regulation will be a potential risk that needs to be considered. This risk can be managed and reduced by following two strategies:

1. Making sure the respective informed consent given by the data subject in the past also covers HARMONY's purposes. This necessitates legal scrutiny of the respectively applied informed consent form(s) to establish whether HARMONY's needs are legally covered sufficiently.
2. A specific new informed consent form needs to be developed early on which will cover future data collection and secondary use within a big data framework (LB, FD). However, newly developed informed consent forms for HARMONY are likely only to be available in 2-3 years from now (CD). There needs to be a well-founded solution for secondary data use until then.

Both current (DPD) and future (GDPR) EU regulations are rather vague, so the risk of legal breach cannot be eliminated completely (CW). The best way to establish legal compliance with any approach chosen by HARMONY will be involving a legal counsel who has **profound experience with the jurisdiction and knowledge of all relevant decisions** in the field (FD).

Legal counsel with experience in jurisdiction

Recruiting legal counsel experienced in jurisdiction might happen through different approaches:

1. Having companies' lawyers check the existing informed consent forms (JA).
2. Requesting HARMONY's Expert Advisory Panel (EAP) to engage a law firm to answer questions on the matter which need to be formulated precisely (FD). In particular this law firm might be asked to consider other legal paths not currently considered by HARMONY, but also by other IMI BD4BO projects dealing with similar issues (CW).

To date the members of HARMONY's EAP have not been nominated yet (LB). To be able to proceed swiftly it might be advisable to engage company lawyers for checking existing informed consent forms (JA).

Conclusions

1. For a full-scale implementation later on the pilot study needs to be fully scalable. No compromises shall be made regarding data selection and handling to provide for a long term perspective.
2. Using pseudonymised data within HARMONY is the most desirable option.
3. Have existing informed consent forms (ICONs) for pilot study data (to be provided by LB) checked by a specialised legal counsel who knows the jurisdiction in the field
4. Collect a number (3) of existing ICONs to request specialist legal advice on
5. Develop a HARMONY-compatible ICON (from 4.) and have it evaluated by a specialised legal counsel who knows the jurisdiction in the field
6. Test pilot with generated random data if necessary
7. Fully anonymise/use fully anonymised data only if there is no other possibility to proceed with the pilot study.

ANNEX 3: Outcomes of the Meeting of WP8 and the Ethics Advisory Board in Vienna, 19/20 June 2017

Ethics Advisory Board (EAB) Member Participants:

- Peter Bauer (PB)
- Inez de Beaufort (IB)
- Federico de Montalvo Jääskeläinen (FM)

WP1 Participant:

- Jesus Maria Hernandez Rivas (JH; IBSAL)

WP2 Participant:

- Lars Bullinger (LB; UULM)

WP3 Participant:

- Rafael Navajo (RN; GMV)

WP8 Participants:

- John Edward Butler-Ransohoff (JB; Bayer)
- Christiane Druml (CD; MUW, chair)
- Klaus Wassermann (KW; MUW, minutes)

Conclusions

8. The HARMONY consortium faces a fundamental dilemma regarding the anonymisation of patient data for secondary use.
    a. To allow for the broadest legally compliant secondary use of data the individual patient data would need to be "fully" anonymised (1).
    b. However, manipulating data in such a way would render it useless for scientific research, e.g., regarding the blurring or deletion of sensitive data, the impossibility to track the evolution of the disease in individual patients/datasets or to complete datasets at a later stage.
9. An alternative to de-identifying data would be to obtain individual patients' consent to the secondary use of their data.
    a. However, the informed consents of most studies performed in previous years hardly ever fully cover data sharing and secondary use to the extent required by HARMONY.

Hence, to promote and facilitate scientifically relevant secondary research on retrospective data, other legal options need to be considered.

b. Furthermore, it should also be considered now to what extent and how data sharing should be addressed by informed consent forms of forthcoming clinical studies for future inclusion in the HARMONY database.

10. FM presented data protection legal aspects in terms of balancing the public interest and individual privacy rights. We take it for granted that the sharing of individual patient information for the purposes of data analysis in the frame of HARMONY will have many benefits for patients. The question is how to do so in a way that protects individual privacy while ensuring that the data is of sufficient quality that the analysis will yield useful and meaningful results. A proper anonymisation (better de-identification) procedure must be both reasonable and defensible, i.e.: de-identification that meets current standards and can therefore be presented to legal authorities as evidence that HARMONY has taken its legal and ethical responsibility towards patients seriously. On the one hand, we should consider the benefits of the project for the health of the community; on the other hand, we should consider also the risks for the personal privacy, so we should balance both interests, which could be fulfilled through *a de-identification method where personal data can be protected without a complete anonymisation*.
11. Regarding identification of single patients by genetic data it was stated that HARMONY is not planning to use germ line genetic data at this moment, but rather data on somatic mutations only. Somatic mutation data does not enable identification of patients.
12. RN presented two de-identification methods that could be applied in HARMONY, both of them could be even complementary. A "hard" and a "soft" method of data de-identification were proposed to resolve the anonymisation dilemma described under conclusion 1. above:
    a. The "hard" method presented focuses on *data record tracking* instead of *patient tracking*. This is a method used by GMV that deletes person identifier information, but will maintain the integrity of the respective dataset (in any case, clinicians only deal with data in which all personal identifiers have already been eliminated). In this approach single datasets will be identifiable, but it will not be possible to trace them back to individual persons.
    b. The "soft" methods presented are the classical pseudonymisation techniques. It could be single or double step. These methods comprise a so-called single or double-brokerage pseudonymisation.

    The emphasis should lie on the issue of *balancing individual rights vs. public interest*. From an ethical perspective, it can be regarded unethical to withhold from the community fighting cancer information that would help improve treatment outcome or would minimise patient's risk by re-using existing data instead of generating more data through the incorporation of more patients into new clinical trials, especially as consent was provided for using data to improve treatment outcomes.

    It was further proposed that data donors' local ethics committees (EC) shall be asked to approve of the "soft" procedure. The EU GDPR calls for a valid anonymisation procedure that takes account "… of all the means reasonably likely to be used …" for identification, also stating

that for that purpose"… account should be taken of all objective factors, such as the costs of and the amount of time required for identification, taking into consideration the available technology at the time of the processing and technological developments." (2, recital 26).

JB stated that companies' lawyers will not endorse any data handling processes adopted by HARMONY. Therefore, an external legal counsel (i.e., a law firm) needs to be commissioned to approve of and take legal responsibility for HARMONY's data handling procedures. A budget will be organized through the CSA Do-It for commissioning a law firm to do this.

13. A paper shall be written laying out the various legal and ethical implications of said "hard" and "soft" de-identification methods proposed. This paper will be conceived by starting from a set of five questions:
    a. What is the main purpose of the HARMONY project?
    b. Why does HARMONY need to maintain a link from data to individual patients?
    c. Why/in what way will data be tracked and/or completed over time?
    d. Which system of maintaining data confidentiality will be applied?
    e. How will HARMONY deal with incidental findings?
14. A recently published paper by the International Committee of Medical Journal Editors (ICMJE) on their new policy on data sharing (3) was brought to the attention of the participants. The paper lays out the ICMJE's future policy of only accepting manuscripts for publication which give a data sharing plan. This policy will come into effect by 1 January 2019 the latest. The assembly recognised that this publication policy currently is of less relevance to HARMONY as, at least concerning the pilot study, secondary use is concerned with studies which have already been published. Moreover, the HARMONY data repository itself can be regarded as an appropriate tool for sharing clinical trials data.
15. HARMONY needs to assign persons' and institutions' formal roles regarding their official functions within the data repository architecture (e.g., data owner, data controller, data processor, etc.). It was agreed that HARMONY itself can't assume any of these roles as it is not a legal entity. Thus, there will be no change of property of the data. Data ownership will remain with the data donors.

For the following **confidential session of the Ethics Advisory Board** on 20 June 2017, 12:00-14:00, all members of WP1, WP2 and WP3 were absent.

16. Inez de Beaufort was unanimously elected as chair of the EAB by the board's members. Prof de Beaufort accepted.
17. The feedback document to IMI's ethics screening procedure was discussed among the members of the EAB. The Board stated that much of the IMI ethics reviewer's comments were actually concerned with conducting clinical trials, not relevant to secondary use of existing data. Apparently there was some misunderstanding about the nature and goals of HARMONY. The Board found other feedback comments to be relevant to a previous state of the discussion within the HARMONY project, while the data de-identification discussions in particular have significantly progressed from the status when the document was written. The Board concluded

that the feedback document needed revision according to the current status of discussion and the detailed plans of implementing confidentiality measures.

18. The EAB recognised the novelty of HARMONY's approach to data processing for biomedical research and agreed that HARMONY shall strive for a balanced view, taking into account the privacy rights of the individual and the substantial public interest in improving treatment of cancer. The Board concluded that such a proportionality of means rules out the use of any absolute de-identification procedures.
19. Accordingly, the Board wrote down their opinion in a letter to HARMONY coordinator JH and handed it over to JH personally after the EAB session was closed.

Next steps for WP8

1. Assist WP1 in revising the HARMONY feedback to the IMI ethics screening procedure according to the recommendations of the Ethics Advisory Board (EAB).
2. Enquire with CSA DO-IT to secure a budget for commissioning a law firm to compile an expert opinion document on HARMONY's intended solution regarding data de-identification.
3. Write a paper laying out the legal and ethical arguments with a balanced view on individual data privacy rights vis-á-vis the public interest of improving cancer treatment. The paper should outline the intended de-identification procedure. This paper will be submitted to the EAB and to external legal counsel (see Nr. 2).
4. A further meeting of the EAB was envisaged for September 2017.

Literature consulted

1. 'EU DPD Article 29 Working Party' opinion on data anonymisation, http://ec.europa.eu/justice/data-protection/article-29/documentation/opinion-recommendation/files/2014/wp216_en.pdf
2. EU General Data Protection Regulation (GDPR, 2016/2018), http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32016R0679
3. Darren B Taichman, Peush Sahni et al., *Data sharing statements for clinical trials: a requirement of the International Committee of Medical Journal Editors*. Lancet 389, June 10, 2017. http://www.sciencedirect.com/science/article/pii/S0140673617312825

ANNEX 4: The EAB's letter to the HARMONY Project Coordinator on IMI's ethics screening

Harmony Coordination Office (IBSAL)

to the hands of Prof. Jesus María Hernández Rivas

Dear Prof. Hernández Rivas:

Having read the document "Ethics Review Procedure / Screening Report" (version 08.12.2016) conveyed to the Ethical Advisory Panel (EAP) on January 11, 2017, this panel acknowledges that this document reflects the status of discussion within the HARMONY consortium at the beginning of the year 2017. After discussing the details of the first pilot Project within HARMONY (AML) this Panel concludes, that the documents need revision to take into consideration the current status of discussion and the detailed plans of implementing measures to guarantee data privacy and security within the HARMONY consortium. This panel acknowledges the effort of the HARMONY consortium to be compliant with all relevant laws and regulations [particularly the general data protection regulation (GDPR)] and will take a position shortly, prior to the start of the AML pilot project, upon receiving an updated document reflecting the current status of discussion.

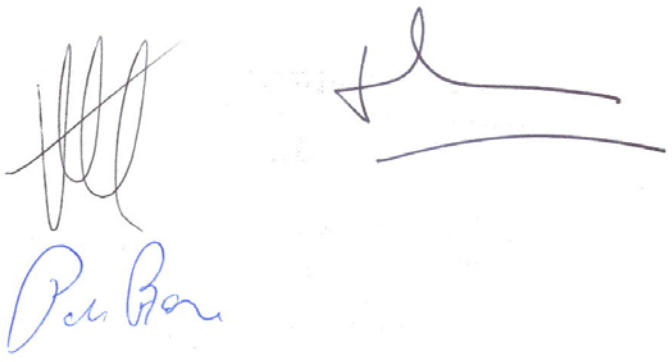
We are facing a new concept of research and we are dealing for the first time with significant new questions that require new, adequate answers. Most of the questions in the document refer to standard clinical trials and are not adequate to deal with Big Data analysis based on secondary use of clinical data. This panel encourages the HARMONY consortium to strive for a balanced view that takes into account the rights of privacy of the individual and the substantial public interest in improving the treatment of hematological malignancies. We consider that anonymization does not require eliminating the risk of identifying an individual, but rather *reducing* the risk of re-identification to a minimum. This proportionality of means rules out the use of any absolute de-identification procedures which would render the clinical data useless, considering for instance the need to track the evolution of the disease or to complete original datasets.

Vienna, June 20th, 2017

Prof. Inez de Beaufort

Prof. Peter Bauer

Prof. Federico de Montalvo



ANNEX 5: Outcomes of the inter-WP face-to-face meeting in Vienna, 18 October 2017

Held at the Josephinum, Medical University of Vienna

Hosts:

- Christiane Druml (CD, MUW, WP8)
- Klaus Wassermann (KW, MUW, WP8)

Participants in person:

- Tamás Bereczky (TB, Leukanet, WP6)
- John Butler (JB, Bayer, WP8)
- Patricia van Dijk (PvD, Novartis, WP1)
- Flemming Moos (FlM, Osborne Clarke, OC)
- Santiago Moralejo (SM, IBSAL, WP1)
- Guillermo Sanz (GS, HULAFE, WP1)
- Ruben Villoria (RV, GMV, WP3/4)

Participants via TC:

- Francesco Cerisoli (FC, EHA, WP7)
- Christina Donatti (CDo, Janssen, WP3/4)
- Enrico Gampieri (EG, UNIBO, WP5; joined for the afternoon)

The Pilot Study

All meeting participants agreed that launching the pilot study currently is HARMONY's highest priority. All technical and managerial prerequisites for the pilot study are reported to be in place. As soon as FIM/Osborne Clarke endorse the jointly (WP3/4, WP8) proposed de-identification procedures the pilot study will be launched in practice.

A time frame of three to four weeks was envisaged for finalising all the relevant preparatory activities.

Anonymising data for the Pilot Study

FIM confirmed opinions expressed earlier by WP8 that with the intended start of HARMONY's pilot study in 2017 the legal data protection framework of the EU Data Protection Directive (DPD, in force until 24 May 2018) and the national data protection laws in the affected countries (i.e. Germany, Italy, UK and the Netherlands) will be relevant. This means that for the pilot study HARMONY needs to comply with the DPD and the mentioned national data protection laws in full, meaning that **any data used in the pilot study will have to be anonymised**. However, the opinion of the Ethical Advisory Board recommending pseudonymizing for the retrospective data collection will be submitted to FIM for consideration as one of the important ethical documents.

FIM/OC will evaluate both the approach of De-Facto-Anonymization recently introduced to WP8 by JB/Bayer and the triple de-identification technique of double-brokerage pseudonymising plus SHA-3 HASH function processing proposed by WP3/4/GMV to establish whether these techniques will provide

valid anonymization in the current legal context.

FIM requested to be sent detail descriptions of HARMONY's **technical data processing techniques, data access management procedures and a list of persons and/or legal entities responsible**.

Type of data used for the Pilot Study

CD and KW expressed concerns that deliverable document D3.02 explicitly mentions that wild-type (WT) genomic data analytics will be used within HARMONY's pilot project. However, according to the definition given in Art. 4 GDPR, "Personal Data" include the **physical, physiological and genetic identity** of a natural person.

Therefore, including respective data fields will potentially put the proposed De-Facto-Anonymization approach for the pilot study at risk. GS and SM acknowledged these concerns and proposed to edit respective passages in both D3.02 and HARMONY's Description of Actions (DoA).

Technical implementation of the Pilot Study

The group discussed responsibilities for data handling and management. In particular, these roles were proposed:

- **Data controller**: Jesus Hernandez/IBSAL/LaFe
- **Data processor**: Gastone Castellani/UNIBO (CNAF)
- **Data custodian** (no official legal term): the hospitals and working groups providing the data (e.g. Lars Bullinger for AMLSG)

WP3/4's documents describing details of data processing and management procedures are still in a drafting stage. These documents will be provided to WP8 and to FIM as soon as they are finally approved within WP3/4.

(Post-meeting note by SM: There might be a misunderstanding regarding the reference to „wild-type (WT)" in deliverable 3.02. WT values versus MT (mutant type) only means that there is no mutation in the IDH2 gene. It can be substituted for terms such as 'standard version of the protein', 'no change found', or anything similar meaning that the patient's protein has not undergone any change with respect to the reference sequence. It does not imply any genetic information able to identify a patient.)

The Double-Brokerage Pseudonymization Paradigm

Applying Double-brokerage pseudonymization techniques, with the option of additional Hash (SHA-3) coding, has been proposed for the sustainable implementation of the HARMONY research platform. This phase of HARMONY will fall under the EU General Data Protection Regulation (GDPR) which will replace the current DPD legislation and the implementing national laws by 25 May 2018.

The GDPR will provide for Data Pseudonymization for research purposes

FIM confirmed that under the upcoming regime of the GDPR the use of pseudonymised personal health

data without informed consent for research purposes can in general be permissible. However, this will still require a respective allowance in either EU or Member State's national laws. For the time being, the GDPR itself or other EU legislation does not provide for such an permission. Art. 9 para. 2 lit. j) GDPR only contains an opening clause which will enable EU Member States to establish their own legislation to allow a use of personal health data for research purposes, provided that the requirements enshrined in Art. 89 para. 1 GDPR are taken into account.

Member states' implementation procedures are currently in progress. Some member states have already put respective legislation in place whereas others haven't yet started doing so. FIM reported that e.g. Germany and likely also the UK are going to have a research-friendly legislation in this respect (i.e. providing for a permission to use personal health data for research purposes without consent). Other Member States might not provide for such permission. FIM stated that member states' bureaus of Osborne Clarke will monitor the legal situation and will report on progress accordingly.

FIM recommended when launching the sustainable (post-pilot) phase of HARMONY, that all provisions of the GDPR – and the relevant national data protection laws which come into force on25 May 2018 – should be taken into account no matter when this phase starts. This way HARMONY will continue to have a clear legal framework for its activities. Certainly, in case the launch should be before 25 May 2018, also the current legal framework (DPD and existing Member State Laws) would need to be adhered to.

Technical implementation of the Double-Brokerage Pseudonymization paradigm

RV reported that the first stage of pseudonymization will be provided by the University of Ulm, the second stage will be performed by SYNAPSE. CDo suggested to compile a guidance document to the data custodians on procedures to de-identify their data prior to transferring to HARMONY. SM confirmed such a document will be produced and provided for review.

WP3/4's documents describing details of data processing and management procedures are still in a drafting stage. These documents will be provided to WP8 and to FIM as soon as they are finally approved within WP3/4.

HARMONY's Informed Consent Template

HARMONY's policy is providing an informed consent form (ICF) for every intended **secondary data use** in the future (i.e., for "prospective data"). For this purpose, a draft ICF has been developed by WP8. The draft document was presented to the group by CD. The presentation is an annex to these minutes.

FIM recommended that in order to particularly comply with Art. 7 GDPR and experiences with patient-favouring legal scrutiny the ICF should be reviewed by Osborne Clarke.

TB requested to include patient representatives (WP6) in the review process of HARMONY's ICF. He also stated that ultimately, patients will be interested in their data to be re-identified. Thus, TB suggested including a passage in the ICF to cater for a possible re-identification.

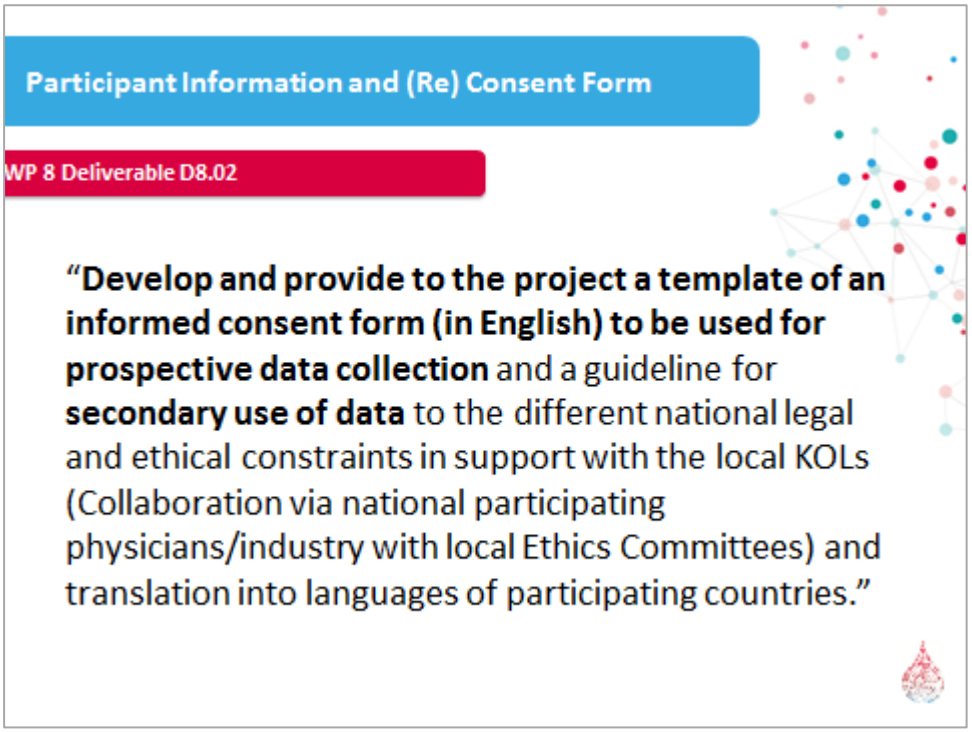
FIM asked whether there might be implications regarding the EU Clinical Trials Regulation (CTR) with presenting the HARMONY ICF together with the primary study's ICF for the patient to sign. CD and PvD

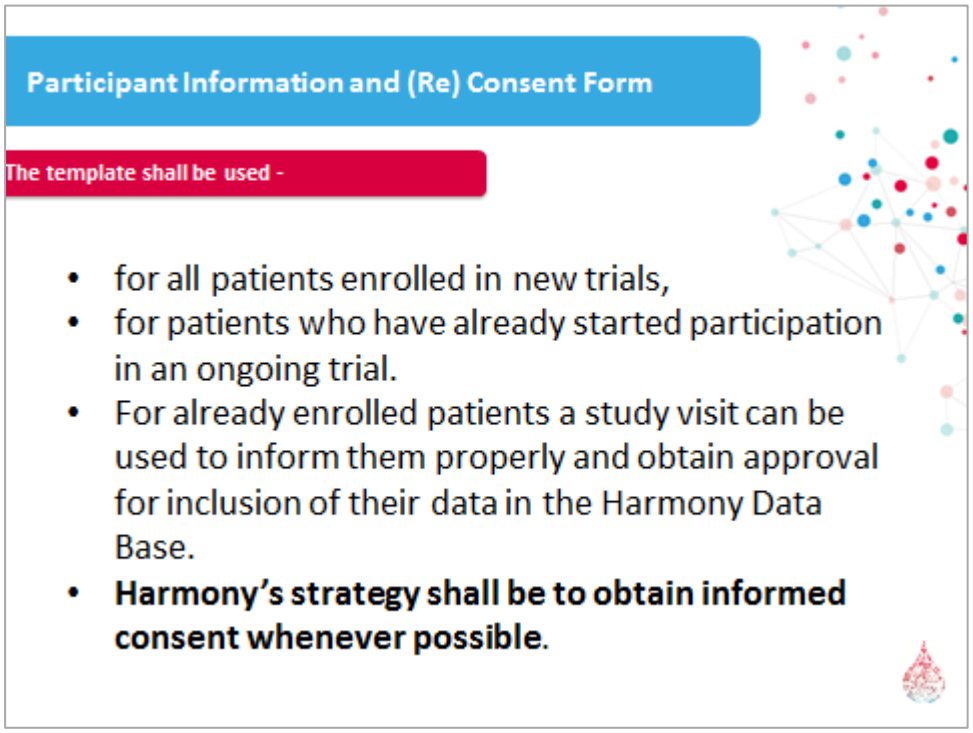
responded that as HARMONY is only interested in **secondary use** of the (prospective) data it will not be involved in any primary clinical trials themselves.

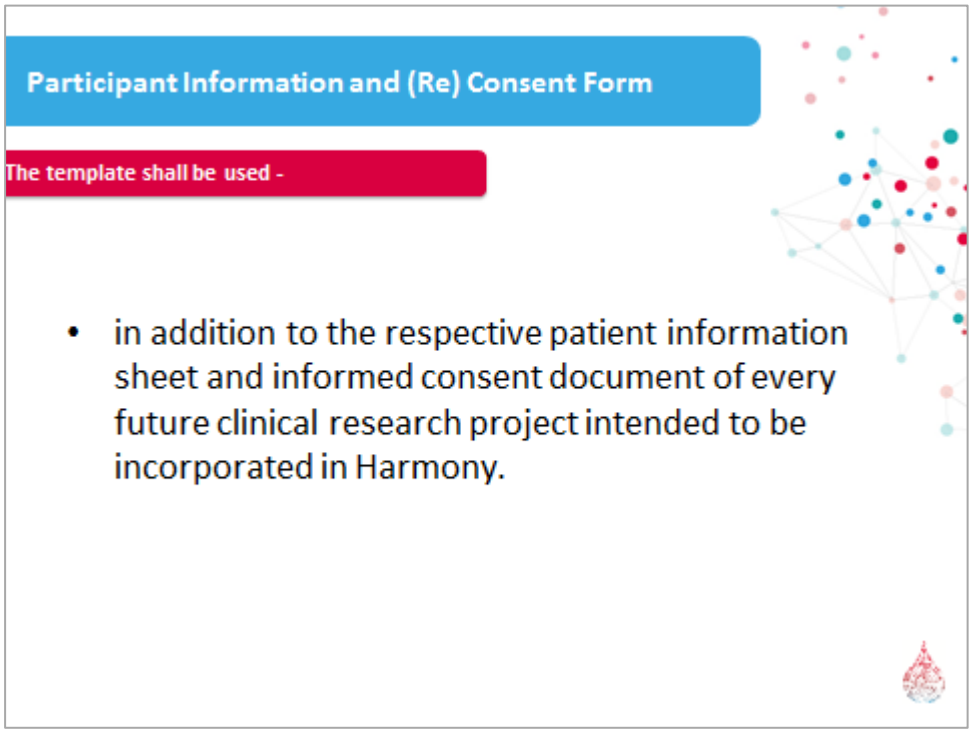
Next steps

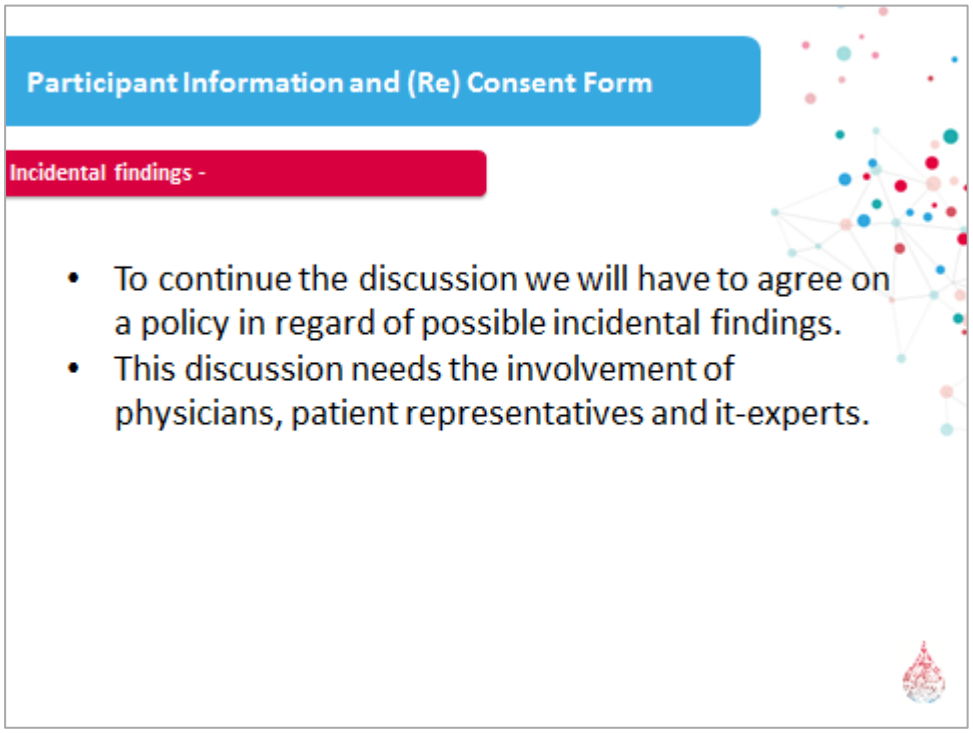
1. KW will mark parts of concern in D3.02 and send the edited document to RV and SM.
    a. RV (WP3/4) will adapt D3.02 accordingly.
    b. SM (WP1) will adapt the DoA accordingly.
2. FIM will share a list of Osborne Clarke's additional requirements for proceeding with their reviewing activities.
3. WP7 will establish how HARMONY's dissemination activities will include patient groups.
4. RV (WP3/4) will provide FIM and WP8 with documents on:
    a. Technical details on HARMONY's data processing (double-brokerage pseudonymization/de-facto anonymization, SHA-3 technique) – in particular as they shall be applied to the data used in the pilot study
    b. Details on data access management procedures
    c. A specification of which persons/legal entities are responsible for HARMONY's data processing activities, most importantly the HARMONY database itself
    d. A data processing and management risk analysis
5. WP1/WP8 will provide FIM with the EAB's opinion document
6. SM will brief Jesus Hernandez to contact the "Spanish EFPIA" and request information on the status of the Spanish GDPR implementation (Art. 89 GDPR).
    a. SM will send the documents on GDPR implementation in Spain to FIM.
7. SM/PMO to provide a guidance document on the practicalities of the double-brokerage pseudonymization techniques to:
    a. WP8 for review
    b. The respective data custodians as a guidance
8. HARMONY's draft Informed Consent Template will be edited to:
    a. Mention an option of re-identifying individual study participants (TB/PvD)
    b. Assure better compliance with Art. 7 GDPR (FIM)
9. A next meeting of a similar group of representatives will be called to discuss in detail FIM's views on the documents provided.

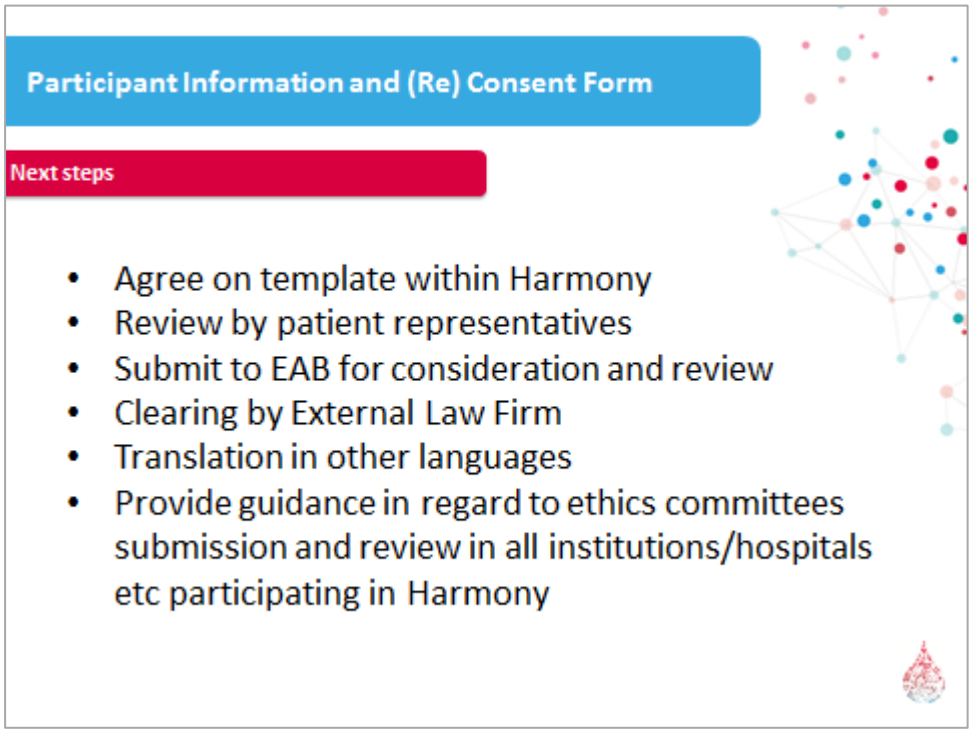
CD's Presentation on HARMONY's Informed Consent Template











Ethics Committees in the EU Member States

Country	Inhabitants in 1,000*	Number of ethics committees*	Number of ethics committees (including local ethics committees)	Ethics committees per million inhabitants
Austria	8,356.7	27		3.23
Belgium	10,741.0	35	215	3.26
Bulgaria	7,602.1	103		13.55
Czech Republic	10,474.6	9	>100	0.86
Cyprus	801.6	1		1.25
Denmark	5,519.3	8		1.45
Estonia	1,340.3	2		1.49
Finland	5,325.1	25		4.69
France	64,105.1	40		0.62
Germany	82,062.2	53		0.65
Greece	11,262.5	1		0.09
Hungary	10,029.9	1		0.10
Ireland	4,517.8	13	40	2.88
Italy	60,090.4	264	>900	4.39
Latvia	2,261.1	5		2.21
Lithuania	3,350.4	2		0.60
Luxembourg	491.7	1		2.03
Malta	412.6	1		2.42
Netherlands	16,481.1	31		1.88
Poland	38,130.3	55		1.44
Portugal	10,631.8	1		0.09
Romania	21,496.7	1		0.05
Slovakia	5,411.1	9	89	1.66
Slovenia	2,053.4	1		0.49
Spain	45,853.0	136		2.97
Sweden	9,259.0	8		0.86
UK	61,612.3	126		2.05

Druml C. et al. *Intensive Care Med 2009; 35: 1636*

Participant Information and (Re) Consent Form

2 ½ pages info & 1 page for signature

HARMONY

26 September 2017

Participant Information and (Re)Consent Form

Project Title:
Version/Date:

Invitation to take part

You are being invited to take part in a medical research project carried out by [name of legal entity conducting the research]. Before you decide whether to participate, it is important you understand why the research is being done and what it would involve for you. Please take the time to read the following information carefully, and discuss it with us and others if you wish.

If anything is not clear, or if you would like more information, please telephone [contact telephone number] to talk to a member of the project team. More information about the [name of legal entity conducting the research] is available at [website address].

Thank you for taking the time to consider taking part in our research study.

What is the purpose of the Research?

[name of legal entity conducting the research] is taking part in a European research project called HARMONY (www.harmony-alliance.eu). The project involves a collaboration between researchers to gather and analyse patient data with the aim of improving the prevention, diagnosis and treatment of various forms of blood cancer. By analysing health data collected from patients, researchers may be able to work out why some people develop particular blood cancers while others do not. When conducting the

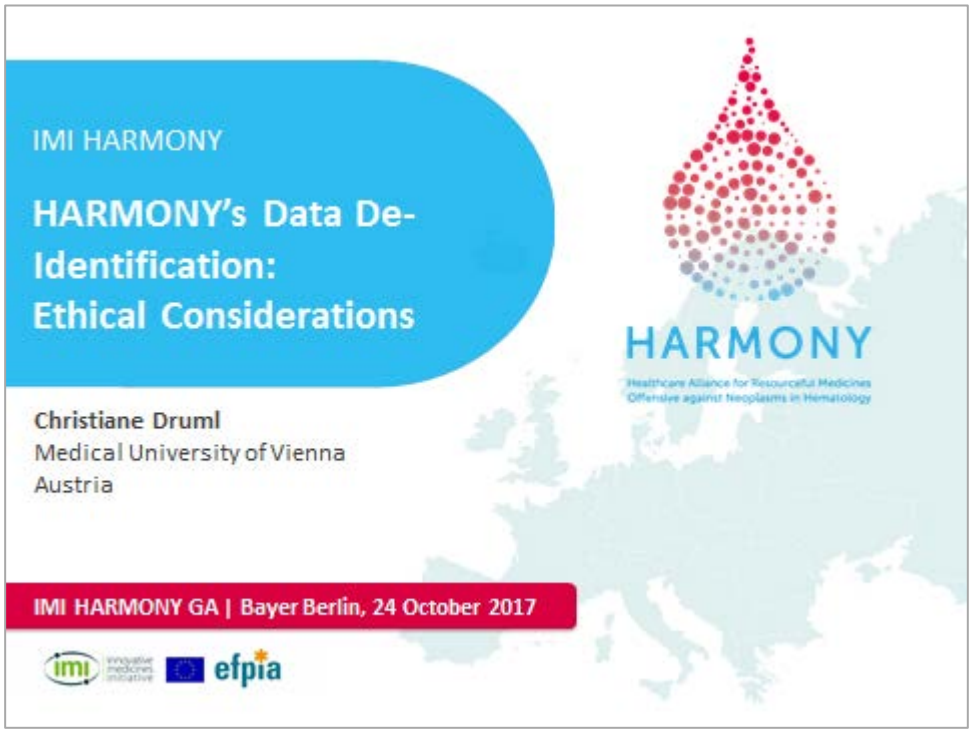
HARMONY

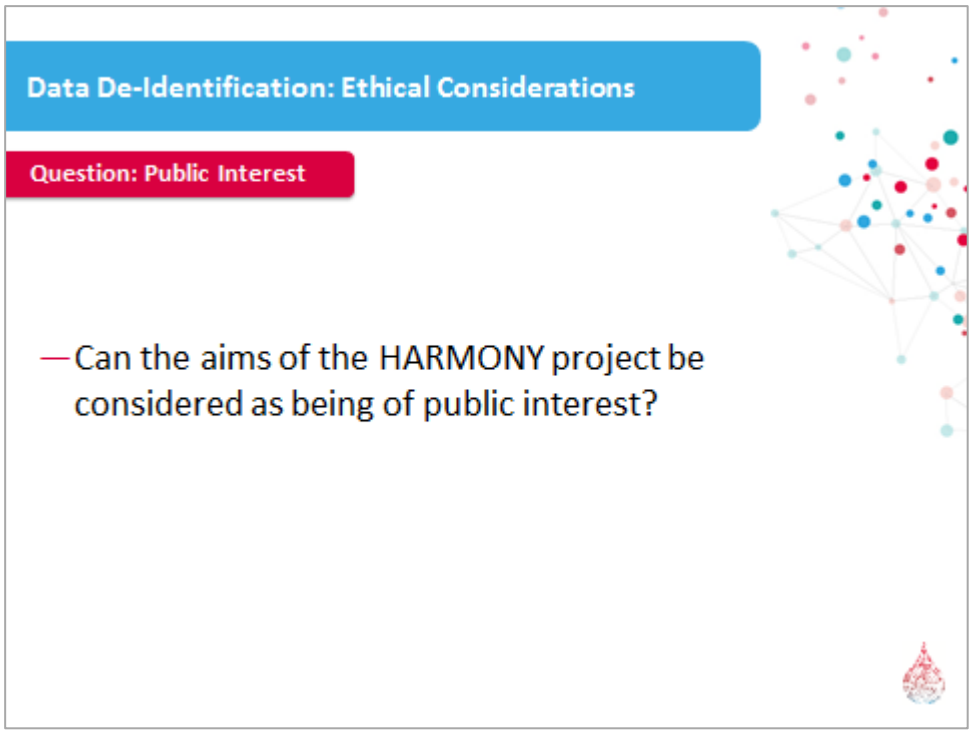
Participant Information and (Re) Consent Form

Next steps - Resumé of 18.10.2017

- Organise a meeting involving WP8 physicians, patient representatives and it-experts (and external lawyer) to clarify:
  - Patient's rights (withdrawal, *correction of data*?)

ANNEX 6: The EAB's position on HARMONY'S data processing approach





HARMONY

Data De-Identification: Ethical Considerations

The EAB's Position on Public Interest

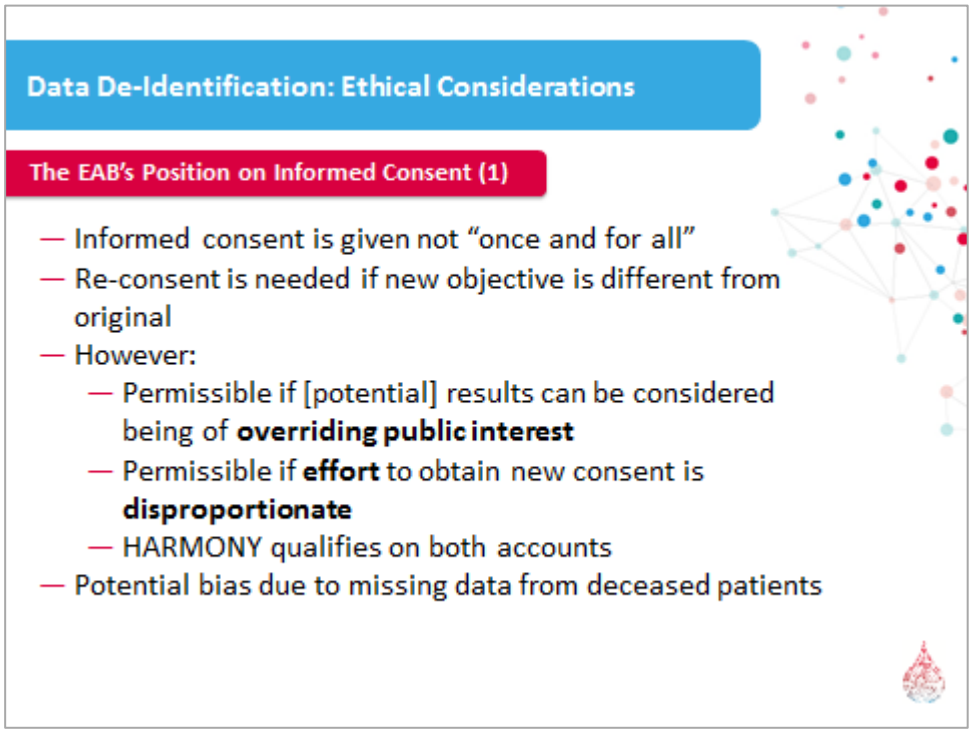
- Undeniable scientific interest
- Addresses very serious unmet needs in cancer treatment
- Prioritises the interest and welfare of patients
- Evaluates effectiveness of medical treatment and protocols
- Helps with determining more relevant diagnoses
- Supports finding more cost-effective treatments
- Helps with developing innovative pharmaceuticals
- Supports progress of personalised/precision medicine

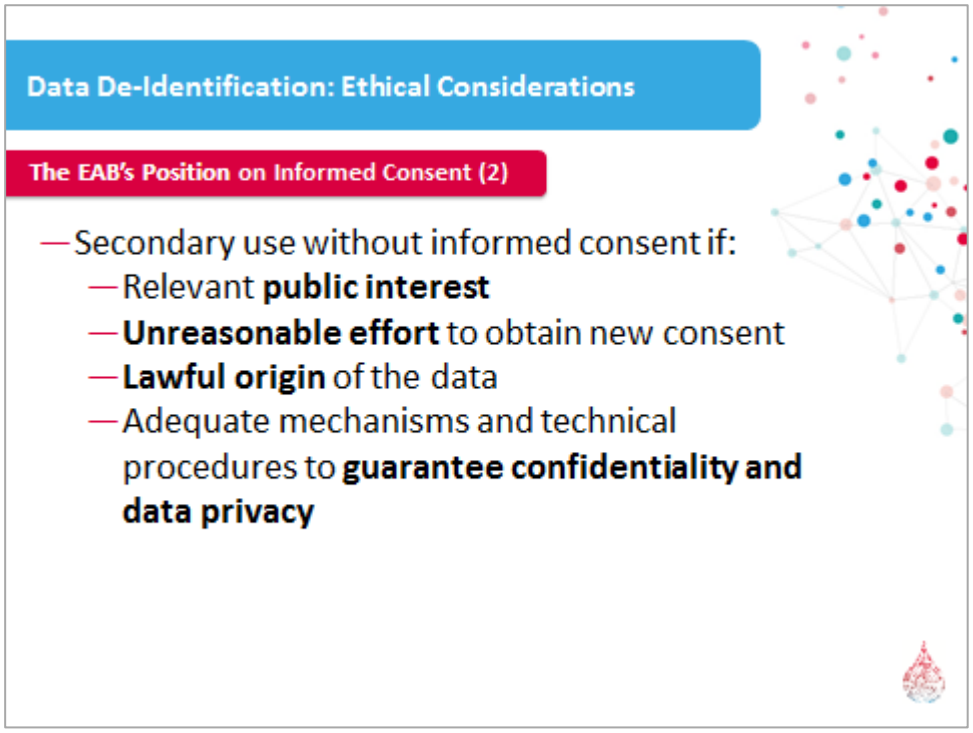
- Processing of personal data must implement confidentiality and privacy safeguards
- Primacy of the human being must be respected

Data De-Identification: Ethical Considerations

Question: Renewed Informed Consent

- Will secondary use of existing data be possible without obtaining a new specific informed consent from data subjects?





HARMONY

Data De-Identification: Ethical Considerations

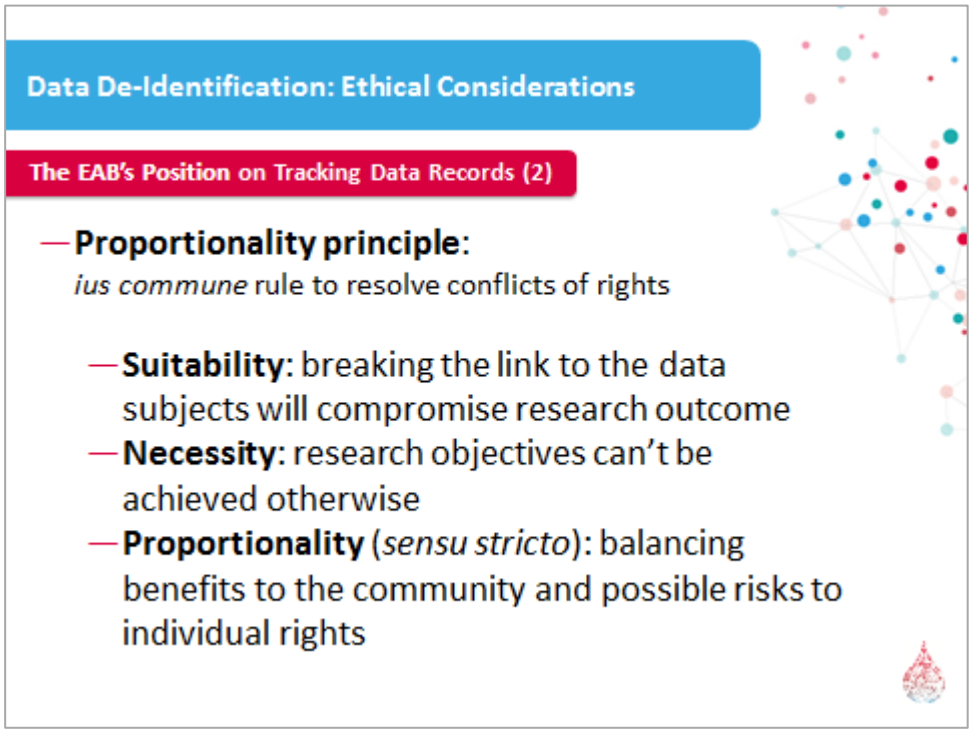
Question: Tracking Data Records

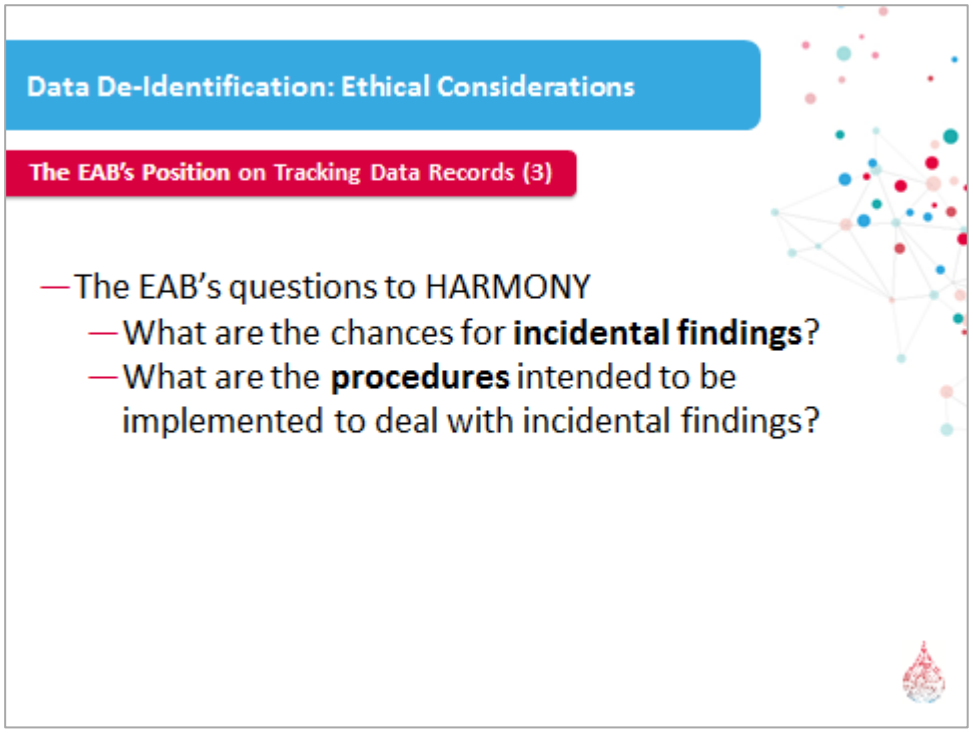
- Will a double-brokerage pseudonymisation paradigm, which provides traceability but still grants a very high degree of data protection, be acceptable from an ethical perspective?

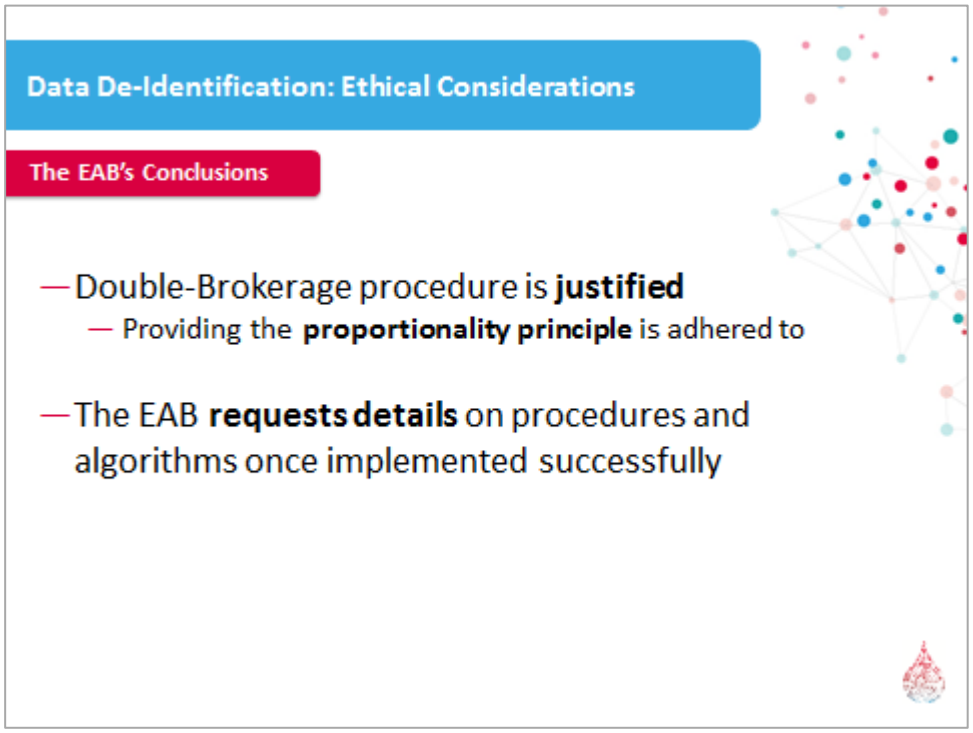
Data De-Identification: Ethical Considerations

The EAB's Position on Tracking Data Records (1)

- Strict anonymisation compromises approach to personalised medicine
- Tracking patients' data is crucial for HARMONY
- **Pseudonymisation** will be introduced by GDPR
- Requirements:
  - Overriding public interest
  - Legitimate origin of the data
  - Compliance with the proportionality principle

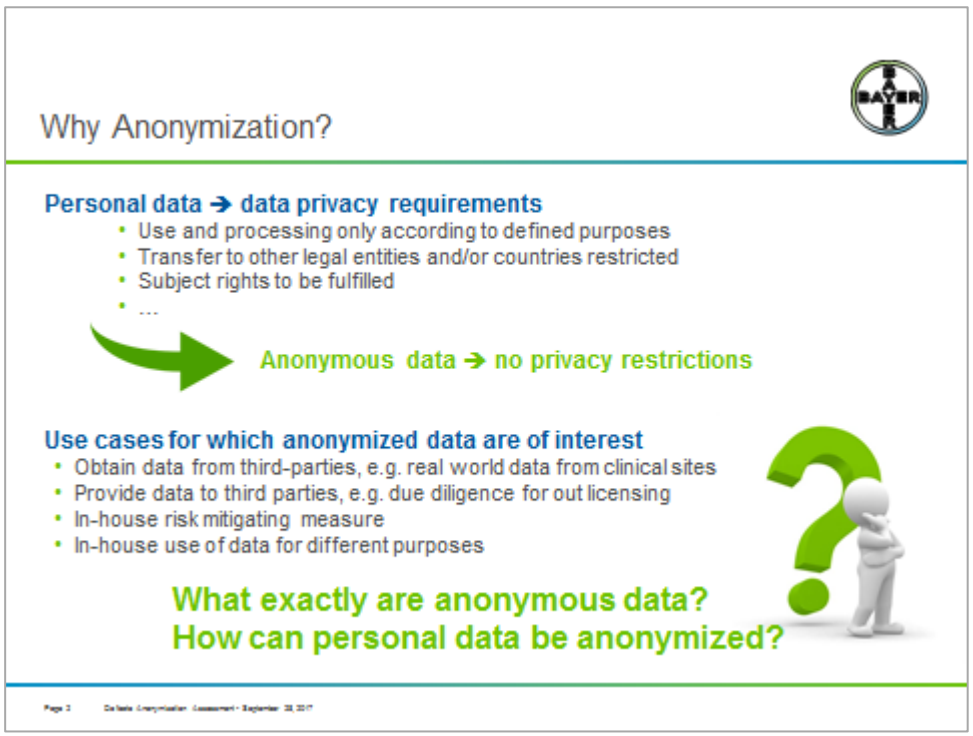






ANNEX 7: BAYER's proposed approach of De-Facto Anonymization

The following slides contain an explanation of the De-Facto-Anonymization approach proposed by Bayer representatives to HARMONY on 28 September 2017. Its purpose is to solve the issue of anonymization of personal data required by the EU Data Protection Directive (Directive 95/46/EC).



Terms and definitions

Personal data: Any information relating to an identified or identifiable natural person; an identifiable natural person is one who can be identified by reference to an identifier like name, identification number, location data, online identifier, factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity (GDPR Art. 4 (1)).

Pseudonymized / key-coded data: Personal data that can no longer be attributed to a specific data subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organizational measures to ensure that the personal data are not attributed to an identified or identifiable natural person (GDPR Art. 4 (5)).

Anonymous data: Information which does not relate to an identified or identifiable natural person. Data is rendered anonymous if the data subject is not or no longer identifiable (GDPR Rec. 26).

De-identified data: Information that does not identify an individual and with respect to which there is no reasonable basis to believe that the information can be used to identify an individual (45 CRF 164.514). Identifiers are e.g. name, locations, dates, email addresses, social security numbers, medical record numbers, health plan beneficiary numbers, account numbers, device identifiers, biometric identifiers, full face photographic and comparable images, other unique identifying number etc.

What are anonymous data?

Anonymous data: Information which does not relate to an identified or identifiable natural person. Data is rendered anonymous if the data subject is not or no longer identifiable. To determine whether a natural person is identifiable, account should be taken of all the means reasonably likely to be used such as singling out, either by the controller or by another person to identify the natural person directly or indirectly. (according to GDPR Rec. 26)

Absolute

Fully anonymous data

- *What is it?*
  Data for which a direct or indirect identification of individuals is not possible at all, independent from technical means and additional knowledge
- *What is the problem?*
  Using statistical methods and additional data sources which become more and more available, one can identify individuals even on basis of highly aggregated data sets. Absolute anonymous data becomes merely a theoretical concept in the context of research & development.

Theoretical concept

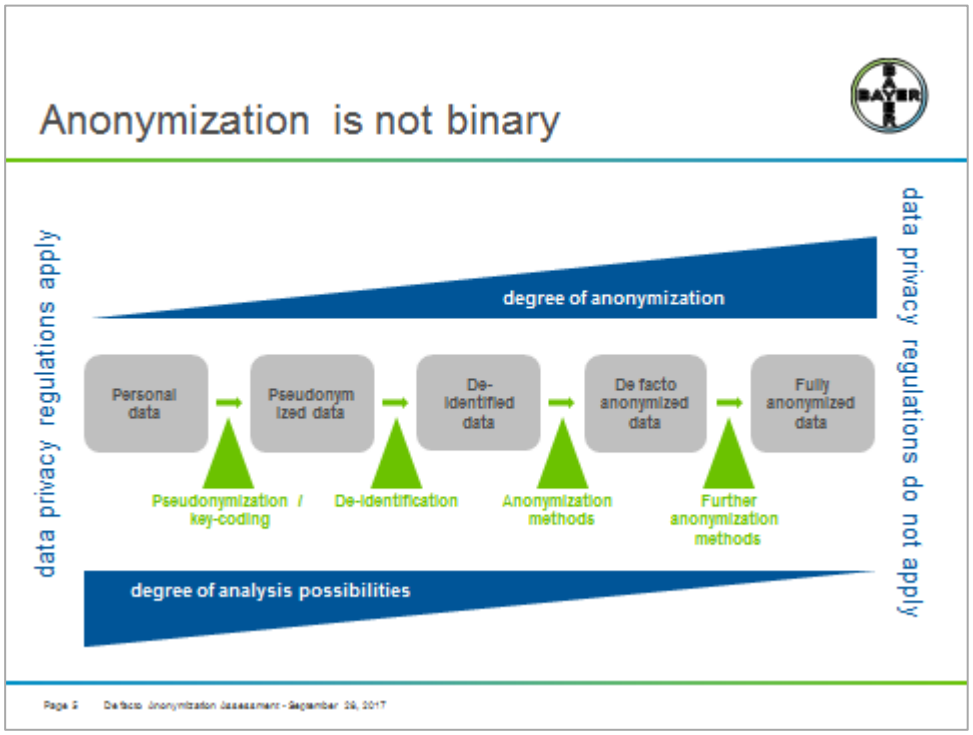
De facto anonymous data*

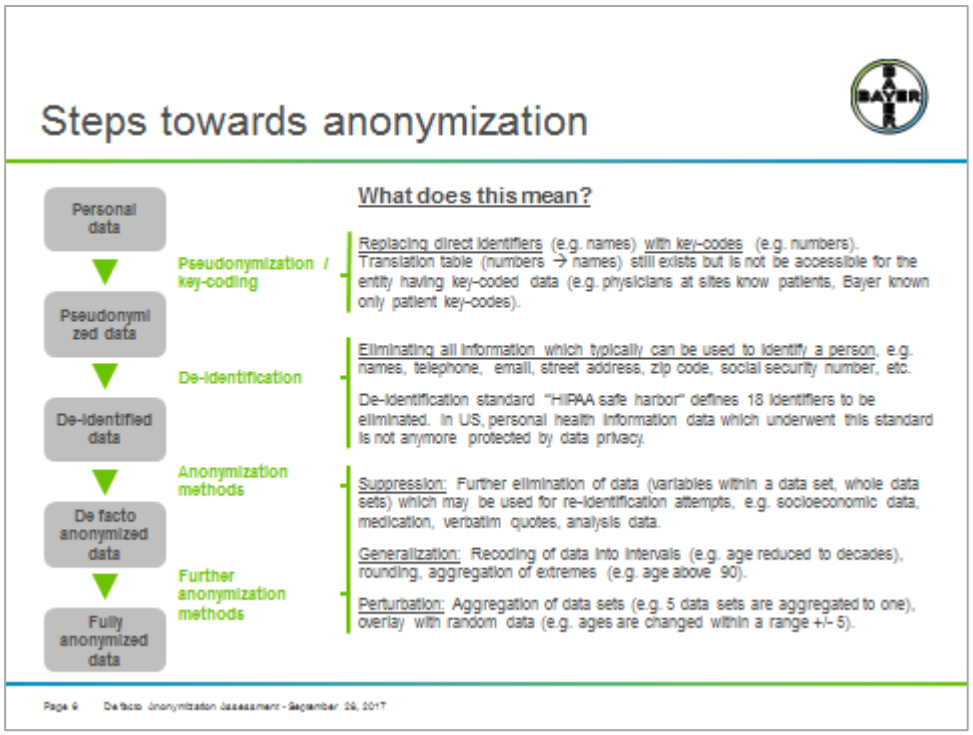
- *What is it?*
  Data for which attributing the individual data to the relevant individual concerned requires *unreasonable effort in terms of time, cost and manpower.*
- *What is the problem?*
  Determining the factual anonymization of a data set is subject to interpretation.

*) Term "de facto anonymized individual data" is used in German Law on Statistics for Federal Purposes § 16 Sec.(6)

Pragmatic approach

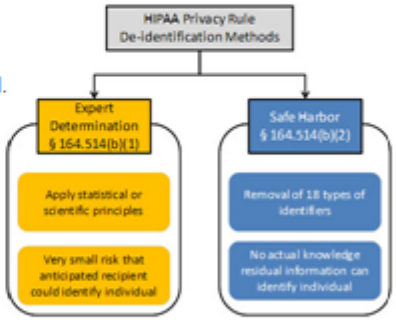
Relative





De-identified data

- HIPAA Privacy Rule (45 CFR § 164.514) provide standards for de-identification of protected health information
  - Expert determination method
  - Safe harbor method
- Satisfying either method demonstrates that a covered entity has met the §164.514 standard.
- De-identified health information is no longer protected by the Privacy Rule.
- Covered entity may assign a code to allow information to be re-identified by the covered entity, provided that certain security measures are met.



*) HIPAA: Health Insurance Portability and Accountability Act (HIPAA). – CFR: Code of Federal Regulations

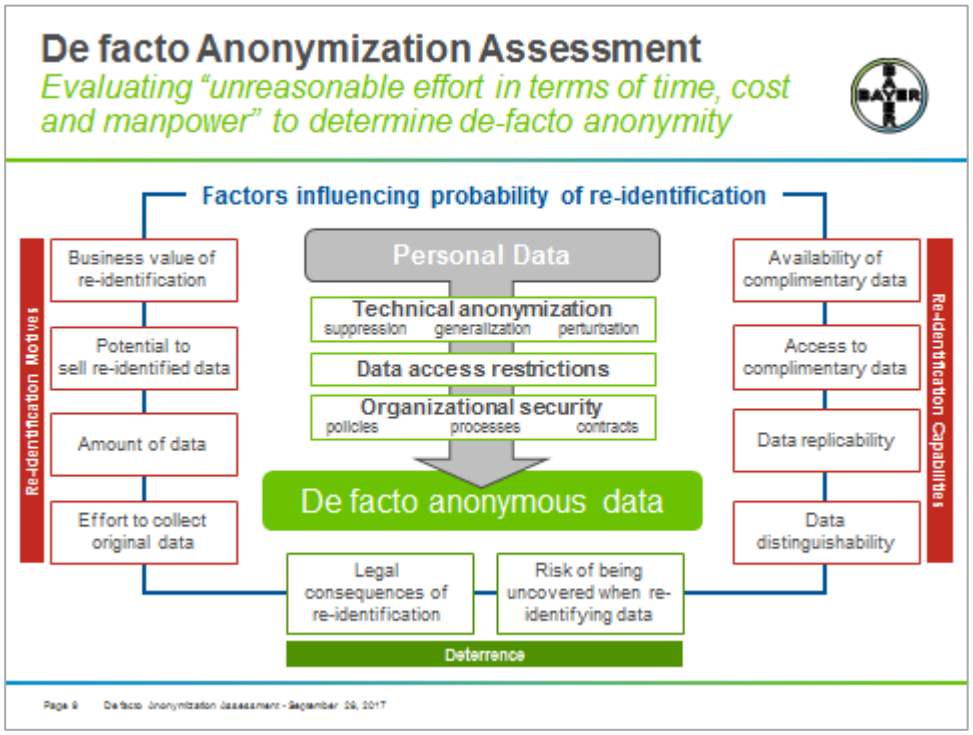
Page 7 De facto Anonymization Assessment - September 29, 2017

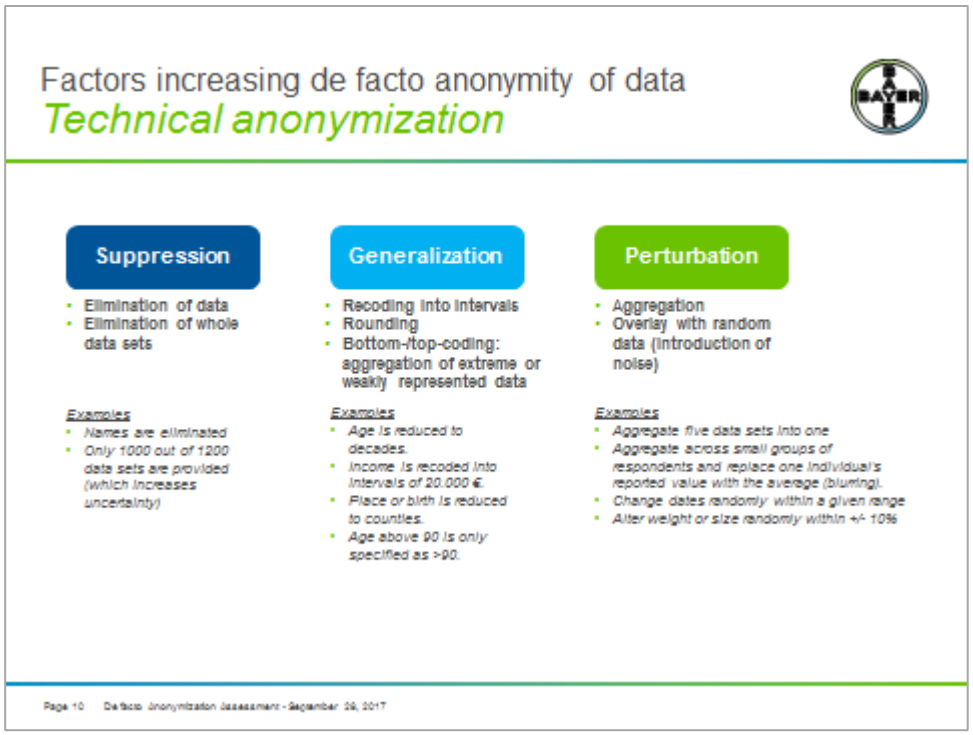
De facto Anonymization Assessment
What is it?

The de facto Anonymization Assessment is a **qualitative evaluation** whether data can be regarded as anonymized **taking into account time, cost and manpower of a potential re-identification attempt.**

- **Scenario-based assessment**
  - Data set characteristics
  - Technical anonymization measures
  - Access to data
  - Organizational measures
  - Capabilities for re-identification
  - Motives for re-identification
  - Deterrent effects
- **Business context specific**
  - Residual risks to be assessed for the specific business context in which the data are to be used
- **No simple algorithm**

Page 8 De facto Anonymization Assessment - September 29, 2017





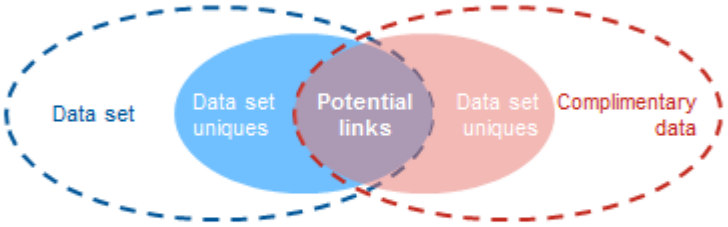
Factors influencing probability of re-identification
Data access and organizational measures

- **Data access restrictions**
  The more restrictive the access to the data, the less are the capabilities for re-identification
  - Limit number of people with access to data
  - Limit download capabilities for full data sets
  - Establish data custodians: Store data at third-party
- **Organizational measures**
  Channel the correct use of data and prevent organizational fault
  - Policies: Define what data use is allowed or prohibited
    - E.g. policy prohibiting to combine data with further data
  - Processes: Ensure data handling in a controlled environment
    - E.g. process to assess whether data obtained from a third-party meets all agreed characteristics (i.e. all anonymization methods have been applied)
  - Contracts: Determines legally binding conditions for data use with a third-party
    - E.g. restrictions regarding data use

Factors influencing probability of re-identification
Capabilities of re-identification

- **Availability of complimentary data**
  Complimentary data is data which can be linked to the anonymized data set and which provides information to identify individuals. The more complimentary data exist – independent from access to that data –, the higher is the risk for re-identification.
- **Access to supplementary data**
  The easier the access to complimentary data is, the higher is the risk for re-identification. Access can be restricted by technical and organizational measures, e.g. technical role concepts, physical access restrictions, policies, contracts, etc.
- **Data replicability**
  Data is replicable if it stays the same when obtained/collected at different times, e.g. birth day, place of birth. Such data can be used for mapping with other data sources / complimentary data. High data replicability increases the risk of re-identification.
- **Data distinguishability**
  Data distinguishability means that data is highly specific to an individual, e.g. fingerprint or retina.

Re-identification principles



Possibility for re-identification increases with:

- Availability of and access to complimentary data
- Amount of potential links / overlapping data
- Replicability and distinguishability of data

Page 13 De facto Anonymization Assessment - September 29, 2017

Factors influencing probability of re-identification
Motives for re-identification

- **Business value of re-identification**
  If knowledge on individuals provide additional value – e.g. for direct marketing purposes –, this increases
- **Potential to sell re-identified data**
  Similar to criteria above, but focus on general market interest to obtain knowledge on individuals.
- **Amount of data**
  The more data exist and, therefore, the more individuals can potentially be re-identified, and the higher may be the benefits regarding two aspects above.
- **Effort for collect original data**
  The higher the effort to obtain the information on individuals oneself, the higher the motivation to try a re-identification.

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Factors influencing probability of re-identification
Deterrence from re-identification

- **Legal consequences of re-identification**
  The more severe the legal consequences of a re-identification (attempt) are, the lower the risk for re-identification.
- **Risk of being uncovered when re-identifying data**
  If re-identification will be identified with a high probability, and at the same time legal or other consequences are expected (e.g. reputational damage), the lower the risk of re-identification.

De facto Anonymization Assessment
How to perform the assessment

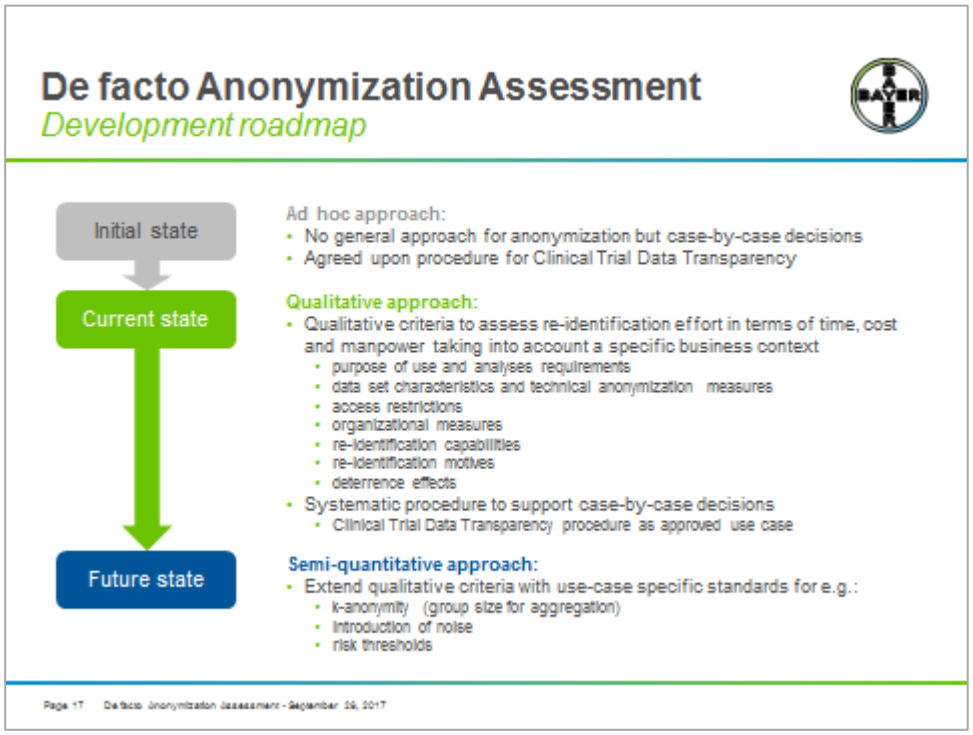
Define responsible function
- Business representative and data privacy manager
- If required: statistician

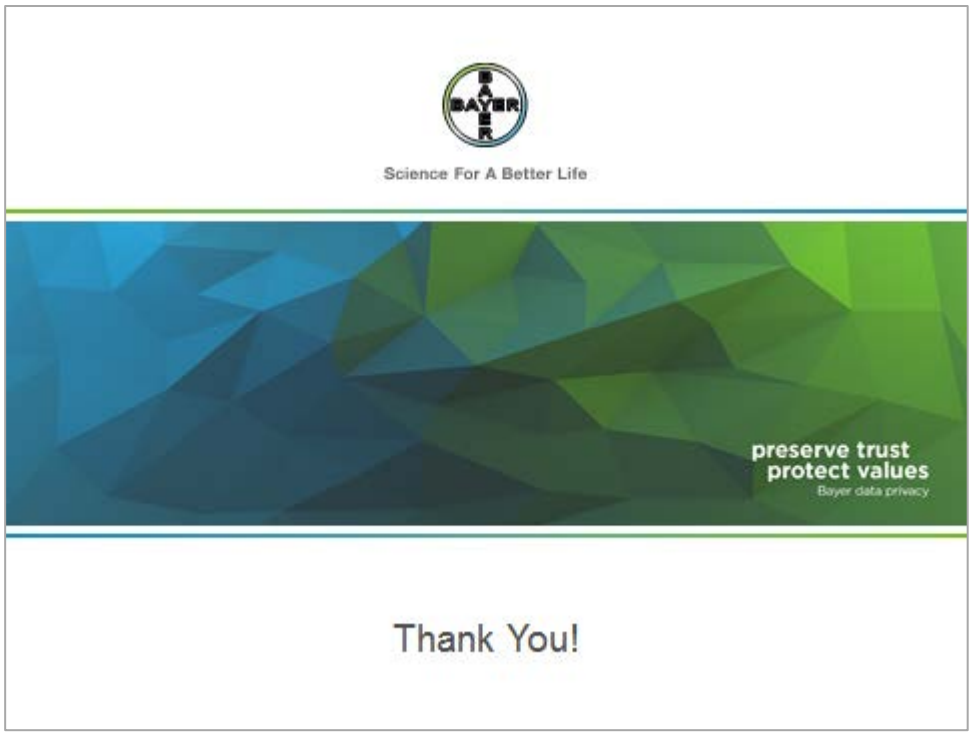
Describe the scenario
- Determine specific business context
  - For which purpose is the data to be used?
  - What are minimum requirements regarding data analyses?
- Identify dataset characteristics
  - Amount of data, type of data
  - Data replicability, distinguishability
- Identify anonymization measures which retain analysis requirements
  - Technical measures (suppression, generalization, perturbation)
- Identify organizational safeguards
  - Access restrictions (e.g. onsite access management, custodians)
  - Contracts, policies, processes

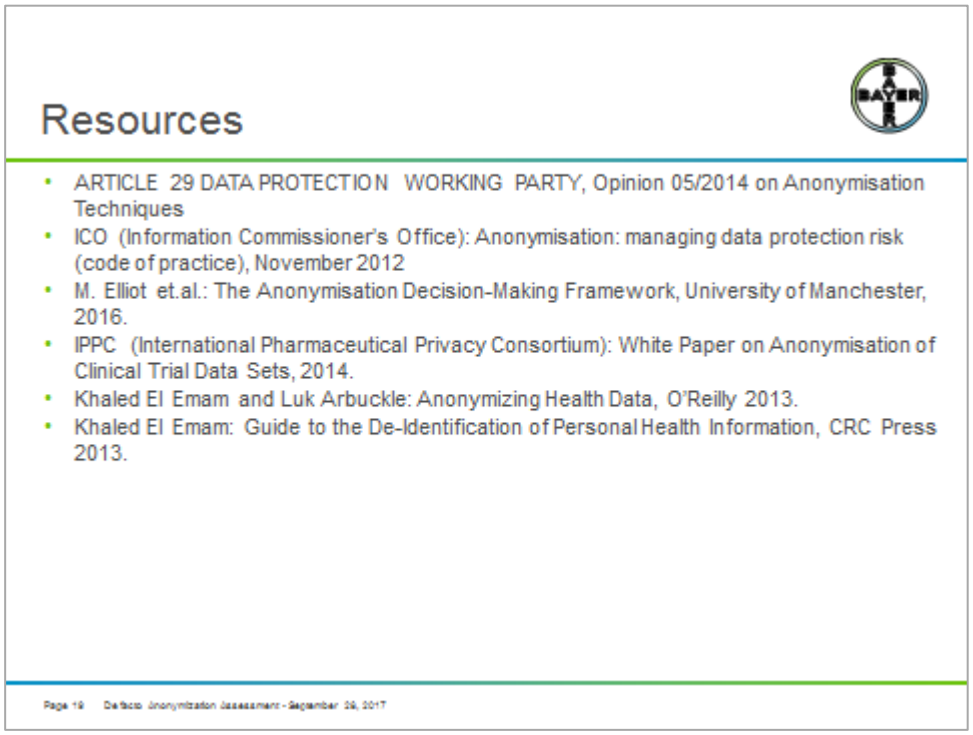
Assess probability of re-identification
- Balance security measures against re-identification motives and capabilities and deterrent effects
- Assess residual risk for re-identification

Document assessment result

Assessment template







Resources

- ARTICLE 29 DATA PROTECTION WORKING PARTY, Opinion 05/2014 on Anonymisation Techniques
- ICO (Information Commissioner's Office): Anonymisation: managing data protection risk (code of practice), November 2012
- M. Elliot et.al.: The Anonymisation Decision-Making Framework, University of Manchester, 2016.
- IPPC (International Pharmaceutical Privacy Consortium): White Paper on Anonymisation of Clinical Trial Data Sets, 2014.
- Khaled El Emam and Luk Arbuckle: Anonymizing Health Data, O'Reilly 2013.
- Khaled El Emam: Guide to the De-Identification of Personal Health Information, CRC Press 2013.

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ANNEX 8: Osborne Clarke's (ELF) memo on data protection law compliance of HARMONY'S Pilot Study

The following three pages present Osborne Clarke's Memo's Executive Summary on HARMONY's pilot study's data protection law compliance dates from 4 December 2017. It represents the first amendment of the initial draft sent out by Osborne Clarke on 17 November 2017. This document was shared with the HARMONY Steering Committee by the PMO on 5 December 2017.

Memo

An	Dr. Patricia van Dijck; Dr. Christiane Druml; Jesus Maria Fernandez	**Von**	Dr. Flemming Moos
Cc	Klaus Wassermann; Dr. John-Edward Butler-Ransohoff	**Büro**	Reeperbahn 1 D-20359 Hamburg
Matter Nr.	1078430/G3346036	**Datum**	17 November 2017

Data Protection law compliance of the HARMONY Pilot Study

The Harmony Consortium has asked us to assess whether the planned Pilot Study within the Harmony project complies with currently applicable data protection laws on EU level and in the relevant Member States.

A Executive Summary

Our assessment can be summarized as follows:

1. **It is possible according to our opinion to design the Pilot Study in a way that it complies with currently applicable EU and Member State data protection laws. For this, it is required that the patient data that shall be used in the Pilot Study are anonymized.**

2. **We think that an anonymization of the patient data sets is permissible, because in our view it does not require a statutory permission or consent from the concerned patient. Even if a stricter view is taken and a legal basis is considered to be necessary, we think that the anonymization could be justified thereunder, although we can also not complete rule out a remote risk that a competent DPA or court might arrive at a different conclusion.**

3. **It is a requirement, that the statutory permission / consent of the concerned individual justifying respectively regulating the original processing of personal data does not prohibit the anonymization / secondary use of the anonymized data. With**

respect to the data sets to be provided from the University of Ulm we think that there are valid arguments that this is not the case.

4. In order to qualify the data sets as anonymous in terms of applicable data protection rules, we consider it sufficient when the data is rendered de-facto anonymous. This is the case if the concerned individual can only be identified with a disproportionate amount of time, expense and labour. We do not consider it necessary to absolutely anonymize the data in the sense that identification is absolutely impossible.

5. In order to safeguard an anonymization of the patient data in this sense, the design of the planned Pilot Study must be adapted. Especially, the following measures must be taken:

   - It must be safeguarded that the patient data to be used in the Pilot Study cannot be linked back to the concerned patient; i.e. it is not sufficient to pseudonymize the data. Particularly, neither the data provider nor the Trusted Third Party (TTP) must create a reference table in which the number of a data set/patient is linked with his/her name.

   - The data must be (fully) anonymized by the data provider or by a service provider acting on behalf of the data provider. This means that the Harmony Consortium must not receive any personal patient data. Therefore, it would not be sufficient to anonymize the data only during the data intake process by the Harmony Consortium. Otherwise, the data would qualify as personal data for the Consortium.

   - According to our understanding it is theoretically possible for a data provider to identify a concerned patient by matching the (de-facto) anonymous data set used in the Pilot Study with another (e.g. the original) data set of the patient because the data is still unique enough. It is necessary to prevent this scenario, as this would turn the (supposed) anonymous data into personal data (for the data provider but arguably also for HARMONY).

     In order to avoid this, we consider it necessary but also sufficient to conclude contracts with all recipients of the data by which they are obliged (1) not to match any data set with any (existing) data set they have in their capacity as data provider, (2) store the Harmony data sets separately from other (personal) data sets, (3) not to publish the received Harmony data sets (neither in journals) and (4) not to transfer or make available any Harmony data to a third party.

These contracts should inter alia include severe sanctions and penalties for any of such actions. Nevertheless, a risk remains that a competent DPA or a court would come to the finding that these contractual measures are not sufficient; especially in the case the recipient of the data has already a corresponding data set (e.g. if the data provider receives a data set from Harmony which this data provider has provided to Harmony and the data provider still has the original (personal) data set).

- Contracts with data providers (and depending on its role also with the TTP) must be concluded by which the data providers (and maybe the TTP) are obliged to apply certain anonymization techniques in order to ensure that (1) only (de-facto) anonymous data is provided by them, (2) they comply with all data protection laws in their area of responsibility (especially re. the anonymization and that the consent/statutory permission justifying/regulating the original data processing do not prohibit the anonymization/secondary use of the pseudonymized data) and (3) assume liability for data protection infringements stemming from their area of responsibility.

- In order to even increase legal certainty, it could be contemplated to consult the competent Data Protection Authority in an effort to receive their evaluation of the envisaged data processing scenario for the pilot study.

* * * * *

ANNEX 9: REFERENCES

These publications contain the guiding principles and legislation to which the project must adhere:

EU General Data Protection Regulation (GDPR, 2016/2018),
http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32016R0679

EU Data Protection Directive (DPD),
http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:31995L0046

'EU DPD Article 29 Working Party' opinion on data anonymisation,
http://ec.europa.eu/justice/data-protection/article-29/documentation/opinion-recommendation/files/2014/wp216_en.pdf

Anne Bahr's and Irene Schlünder's paper on secondary use of research data in Europe,
https://doi.org/10.1093/idpl/ipv018

Darren B Taichman, Peush Sahni et al., *Data sharing statements for clinical trials: a requirement of the International Committee of Medical Journal Editors*. Lancet 389, June 10, 2017.
http://www.sciencedirect.com/science/article/pii/S0140673617312825