

# Framework Regulation



PARELSNOER INITIATIEF

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Parties involved in the String of Pearls Initiative:

- Amsterdam Academic Medical Centre
- Erasmus Medical Centre, Rotterdam
- Leiden University Medical Centre
- Radboud University Nijmegen Medical Centre
- Groningen University Medical Centre
- Maastricht University Medical Centre
- Utrecht University Medical Centre
- VU University Medical Centre, Amsterdam

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# 1 Introduction

Since 2007 the eight Dutch University Medical Centres (UMCs) have been collaborating in the String of Pearls Initiative, the purpose of which is to create an infrastructure in the academic centres for collecting clinical data, including image material, and to set up biobanks at inter-university level. The project primarily addresses the clinical pictures of neurodegenerative diseases, leukaemia, rheumatoid arthritis, inherited bowel cancer, diabetes mellitus, renal failure, cerebro-vascular accident and inflammatory bowel diseases. The scientific data that is created with the assistance of this infrastructure is expected to lead to improvements in the health of patients with the aforementioned conditions and strengthen the economic position of biomedical research in the Netherlands. At present, collaboration in the context of the String of Pearls Initiative is limited to the eight established UMCs, but other hospitals or research institutions may be invited to join in the future. In addition, the activities of the String of Pearls Initiative may be extended to include other clinical pictures in the future.

The String of Pearls project is being carried out under the administrative responsibility of the board of the Dutch Federation of University Medical Centres (NFU). The board of the NFU is made up of the chairs of the boards of the eight university medical centres. Major decisions relating to planning, budgets and underlying principles are taken by the NFU board. Furthermore, every member of the NFU board is directly responsible for the activities of the UMC which he or she represents. This enables developments in the project to be addressed directly by the board members in their own UMC. The NFU has appointed a board of directors consisting of two members which is tasked with handling day-to-day management aspects. The board of directors is responsible for achieving the formulated objectives. The Scientific Director is tasked with reaching consensus on the scientific aspects, the long-term policy and participation by the String of Pearls in new initiatives in Europe and elsewhere. The General Director is responsible for day-to-day management, finance and ICT.

The government has provided a subsidy from the Economic Structure Enhancement Fund for the String of Pearls Initiative. On government level, the Ministry of Education, Culture and Science (OC&W) is responsible for the project and will include the Ministry of Economic Affairs (EZ) and the Ministry of Health, Welfare and Sport (VWS) in the assessment of the project.

In order to ensure effective collaboration between the eight UMCs, it was decided to draw up this Regulation. The Regulation sets out the minimum parameters and requirements which the collaboration will have to meet in order to be able to achieve the objectives of the String of Pearls. It is also intended to offer sufficient guarantees for the donors and other parties involved in implementing the String of Pearls.

## 2 Legal responsibility

In drawing up the regulation an attempt was made to tie in with any existing internal regulations and resources the parties may have and thus respect their autonomy. However, the compilers realise that the conditions for collaboration may in some areas entail changes to a Party's existing set-up. This is inherent in this kind of collaboration.

This Framework Regulation was drawn up taking into account international, European and national legislation and regulations on human rights, privacy, biomedical research and the use of human tissue, as well as the approved regulations applicable to the latter in the context of self-regulation.

### 2.1 International

#### 2.1.1 Personal data

The use of personal data is governed by European Directive 95/46/EC<sup>1</sup>. According to the Directive, medical data constitutes personal data and therefore falls within the scope of the Directive. This privacy directive was implemented in the Netherlands in the Personal Data Protection Act (*Wet Bescherming Persoonsgegevens, Wbp*).

#### 2.1.2 Human tissue

There is still no formal binding regulation in place in Europe on the use of human tissue<sup>2</sup>. The most recent draft of the Declaration of Helsinki, which has not yet been ratified, states that research with identifiable human tissue or identifiable personal data falls within biomedical research involving human subjects, to which the principles of the Declaration apply. However, these principles do not provide a practical guide to the use of human tissue in medical research<sup>3</sup>.

On 15 March 2006 the Council of Europe adopted Recommendation Rec(2006)4 which introduced rules for research with human tissue and associated data<sup>4</sup>. The main reason for adopting this recommendation was concern about access to and the security of data and publicity of cases in which human tissue was used for research purposes without the knowledge and consent of the persons involved. The paramount concern of the Recommendation is therefore to protect the rights and fundamental freedoms of persons whose body material could be used in a research project. The introduction of rules should furthermore help boost confidence in medical practice and research procedures.

Article 11 of the Recommendation states that an intervention to remove human tissue should only be carried out if it complies with the Additional Protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research. Only the latter document has been signed by the Netherlands, although it has not been ratified. The protocol lays down rules for the protection of clinical research subjects. These rules are established in the Netherlands in the Medical Research Involving Human Subjects Act (*Wet medisch onderzoek, WMO*).

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<sup>1</sup> Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

<sup>2</sup> See also E.-B. van Veen, P.H.J. Riegman, W.N.M. Dinjens, et al. TuBaFrost 3: Regulatory and ethical issues on the exchange of residual tissue for research across Europe. EJC 42 (2006)2914-2923.

<sup>3</sup> Version 6 of the Declaration of Helsinki of the World Health Organization, October 2000.

<sup>4</sup> Rec(2006)4: Recommendation of the Committee of Ministers to member states on research on biological materials of human origin (<http://www.coe.int>).

Although the Recommendations of the Council of Europe are not legally binding on the 47 member states of the Council, the European Commission conforms to the Recommendations, as a result of which they can be incorporated into the conditions for European subsidies and set the agenda for research to be subsidised by the Commission.

Also relevant to research with human tissue is Directive 2004/23/EC, recital 18 of which states that human tissue as such may not be used to obtain financial gain<sup>5</sup>. The same provision is included in Article 7 of the Recommendation of the Council of Europe.

## **2.2 The Netherlands**

### **2.2.1 Personal data**

The use of personal data is primarily governed by the Wbp. According to this Act, personal data is data concerning an identified or identifiable person. Anonymous data is therefore not classified as personal data. Data in coded form may in principle be considered to be personal data, however. In addition, the Wbp defines medical data as personal data.

The Wbp sets out requirements for the processing and use of personal data. The processing of medical data is generally prohibited, although hospitals are exempt from this prohibition. The Wbp sets out the following requirements for the use of personal data:

- Personal data may only be collected and processed if there is a good reason to do so or if the subject of the data has given consent for his/her data to be used;
- No more data may be processed than is strictly necessary for the purpose for which it was collected;
- The data may not be kept for longer than is necessary;
- Appropriate technical and organisational measures must have been taken to protect the data;
- The subject of the data must generally be informed about the processing of his/her data.

In certain cases, processing of such data must be reported to the Dutch Data Protection Authority (DPA) which supervises compliance with the Wbp. It can also be reported to the organisation's personal data protection officer (in this case at the UMC).

The processing and use of medical and personal data is also governed by the Medical Treatments Contracts Act (*Wet op de geneeskundige behandelingsovereenkomst*, Wgbo)<sup>6</sup>. Section 88 of the Individual Healthcare Professions Act (*Wet op de Beroepen in de Individuele Gezondheidszorg*) requires certain professional groups including doctors and nurses to maintain medical confidentiality. A more detailed description of medical confidentiality is provided in Section 7:457 of the Wgbo<sup>7</sup>. Medical confidentiality means that the practitioner may not disclose any data in the medical file to others without the patient's consent.

An exception is made for the provision or viewing of such data for statistical or scientific research for public health reasons, although the Act only permits this in cases where consent cannot or should not be obtained because of the nature and objective of the research. Biobanks do not, however, focus on research exclusively involving medical data; human tissue plays a crucial role in such research. Because the String of Pearls Initiative concerns human tissue that is collected prospectively, the patient or his/her

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<sup>5</sup> Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. 31 March 2004

<sup>6</sup> Article 7:457 of the Dutch Civil Code (BW).

<sup>7</sup> This section also imposes the duty to maintain confidentiality at the institution at which the healthcare professional works.

representative can always be asked for their consent. This also applies to the use of the necessary medical data.

Pursuant to the Wbp, the form of data chosen for research purposes must always guarantee minimal infringement of the privacy of the person concerned. In other words, anonymous data must be used wherever possible. This is not practical from the point of view of biobanks, since the data must be able to be related to the human tissue and it is not inconceivable that the biobank will want to supplement the existing collection with new human tissue and with more recent data from the patient treatment file. For this reason the data must be encoded in such a way that the privacy of the donor is protected as much as possible.

### **2.2.2 Human tissue**

In the Netherlands, the use of so-called residual tissue which has been removed for a purpose other than scientific research (e.g. for diagnosis or treatment) is governed by the code of conduct for Proper Secondary use of Human Tissue<sup>8</sup>. However, there are no laws or regulations in the Netherlands governing the use of human tissue that is collected for use in future scientific research. The removal of human tissue from subjects participating in medical research is regulated by the Medical Research Involving Human Subjects Act (WMO)<sup>9</sup>. This removal falls under the subjection of persons to treatments as referred to in Section 1 of the WMO.

The WMO provides that prior written consent must be obtained from the subject. This consent must be properly informed. The WMO also specifies who is allowed to give consent on behalf of the subject and stipulates that subjects may withdraw from the research at any time. Separate rules are included for research involving children or persons incapable of giving informed consent.

However, the WMO does not effectively cover the removal of human tissue for future research that has not yet been defined and has therefore not yet been described in detail in a research protocol.

### **2.3 By analogy with the WMO**

The following sections of the WMO are relevant to the removal of human tissue in the context of biobank activities such as those being performed under the String of Pearls Initiative.

- Section 1 of the WMO defines research as 'medical research in which persons are subjected to treatment or are required to behave in a certain manner'.
- Section 2 states that the research must be conducted in accordance with a research protocol which has been approved by an authorised medical ethics committee or (in certain cases) by the Central Committee on Research Involving Human Subjects.
- Section 3 sets out the conditions under which the committee may approve the research protocol.

As stated in clause 2.2, the removal of human tissue for research must be regarded as a treatment governed by the Act if it forms part of a medical research study as defined in Section 1 of the WMO. If the research complies with the definition in Section 1, it must be performed in accordance with a research protocol written for that purpose which must have been approved by the MERC or CCMO.

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<sup>8</sup> Code of Conduct: see <http://www.federa.org/documentation>.

<sup>9</sup> Act of 26 February 1998 regulating medical research involving human subjects, last amended on 1 March 2006

The question remains whether removal of human tissue for future research purposes that have not yet been defined should be regarded as treatment forming part of medical research. Although the process of removal is a treatment to which the person is subjected, this treatment in itself does not form part of any research at that point. There is also no verifiable research protocol at this stage.

At the time of the removal the criteria set out in Section 3 of the WMO cannot be verified, so Section 2 of the WMO cannot be complied with either. Once the human tissue is requested for a specific research study, the removal of that material no longer forms part of the research protocol<sup>10</sup>.

It is the task of the legislator, not the String of Pearls Initiative, to formulate the general conditions for biobank activities. On the other hand, it is also in the interest of collaboration in the String of Pearls Initiative to subject the execution of the collaboration to rules ensuring the care, safety and privacy of the individuals involved and responsible management of the human tissue obtained. The WMO provides the most useful guidelines for this. In drawing up this Regulation, it was therefore attempted to tie in with the conditions of the WMO wherever possible and desirable.

The conditions for the removal of human tissue, the disadvantages this entails for the donors concerned, and the objectives, collaboration and procedures of the Pearls have been established in a separate regulation for each Pearl. The donor information to be used by the Pearl and the informed consent forms are annexed to and form part of those regulations.

The regulation for each Pearl will be put before an approved Medical Ethics Committee on that Pearl's behalf. On a local level, the boards of directors of the individual UMCs must approve the activities of each Pearl.

A research protocol is required for each research study undertaken in the String of Pearls Initiative. Human tissue and medical data will only be provided if approval has been given either by a panel of experts set up by each Pearl, the members of which have no involvement in the research to be verified and whose composition and powers are defined, or by a recognised Medical Ethics Committee.

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<sup>10</sup> With regard to the applicability of the WMO to biobank activities, see also the standpoint of the State Secretary of VWS, Policy Letter on Ethics of 7 September 2007, PG/E-2779297, page 22.

### 3 Definitions

- 1) In the Regulation, the following terms have the meanings ascribed to them below:
  - a) Treating Physician: The doctor or medical specialist directly involved in the medical treatment of the Donor or potential Donor under the provisions of the Wgbo.
  - b) Provision: The provision of Human Tissue and Donor Data on behalf of the Parties for Research purposes.
  - c) Findings: The research outcomes that have been scientifically validated and that have a relevant predictive value for current or future treatment of patients.
  - d) Biobank: A collection of Human Tissue managed by a Party or a third party.
  - e) Central Infrastructure: The central facilities in which the accumulated collection of Donor Data of all Parties is stored and in which information about the type and quantity of Human Tissue earmarked for each Pearl is stored by Parties.
  - f) Central Organisation: The String of Pearls has a central organisation to support the activities being carried out by Parties in the context of their collaboration, including the management of the Central Infrastructure.
  - g) Donor: The individual who donates or has donated Human Tissue and Donor Data including for the purposes of the String of Pearls Initiative under the conditions described in this Regulation.
  - h) Donor Data: Pseudonymised medical data, clinical data – including digital image material – and other data of Donors that is relevant to Research, as well as data derived from Human Tissue from Donors.
  - i) Donor Material: Human Tissue that is collected and stored for the objectives of the String of Pearls Initiative.
  - j) Pseudonymised: Personal data that has been processed in such a way that the identity of the Donor concerned cannot be traced by the Researcher, but which still allows the identity of the Donor concerned to be traced by the Party Providing this data. This is done by the Party Providing the data replacing the identifying data of the person concerned with a pseudonym that is unique to each Donor.
  - k) Human Tissue: All the elements removed from the human body which are stored for research purposes in a Biobank. Human Tissue may be residual tissue or material removed specifically for scientific research purposes, including Donor Material.
  - l) Medical Ethics Review Committee (MERC): An approved Medical Ethics Review Committee appointed under the provisions of the Medical Research Involving Human Subjects Act (WMO) having the powers laid down in the Act.
  - m) Research: All the research carried out in the context of the String of Pearls.
  - n) Researcher: A person, company, institution, enterprise or organisation that undertakes Research in accordance with the conditions of this Regulation.
    - i) A Researcher is an internal Researcher if he/she/it forms part of a Pearl and is provided with Donor Data and Donor Material from other Parties within

that Pearl's objective.

ii) All other Researchers are external Researchers.

- o) Disclosure: The disclosure for the purposes of the String of Pearls by or on behalf of Parties of the presence of Human Tissue available from those Parties for Research, as well as the transmission of Donor Data by Parties to the Central Infrastructure.
- p) Pearl: A joint venture focusing on a specific medical condition. A Pearl consists of a Pearl Coordinator and several Pearl Participants who, in the context of the String of Pearls and under the conditions set out in this Regulation and on behalf of the Parties involved, collect and Provide Human Tissue and Donor Data for Research and who are furthermore responsible on behalf of Parties for ensuring that the tasks of a Pearl are carried out as defined in this Regulation.
- q) Pearl Coordinator: The person appointed by the Party with primary responsibility for a Pearl to coordinate collaboration in the Pearl. The Pearl Coordinator is also the Pearl Participant in the Party for whom he/she works.
- r) Pearl Participant: A person appointed by a Party to take charge of the execution of the activities of a particular Pearl at that Party and who represents the interests of that Pearl at that Party.
- s) String of Pearls: The collaboration between the Parties under which each of the Parties will Disclose and Provide Human Tissue and Donor Data for Research under the conditions of this regulation.
- t) String of Pearls Management: The board of the Dutch Federation of University Medical Centres.
- u) String of Pearls Board of Directors: The body responsible for day-to-day management of the activities carried out in the context of the String of Pearls and which consists of a general director and a scientific director.
- v) Party(ies): One or more parties connected with this Regulation.
- w) Personal Data: Data concerning an identified person or a person who can be identified without disproportionate time and effort.
- x) Serendipity Findings: Unforeseen results from Research which are not related to the protocol on which the Research is based and which have or may have direct significance for the health of a single Donor or a particular group of Donors.
- y) Representative: The person who is legally entitled to act on behalf of or alongside the Donor.
- z) Scientific Committee: A committee set up or appointed for each Pearl which is responsible for assessing the research protocol of the Research according to the Procedure for the Scientific Committees.

#### **4 Collaboration in the String of Pearls**

- 1) Each of the Parties shall, in accordance with their own internal policy, arrange for the setting up of one or more Biobanks which can be used partly or entirely for the purposes of the String of Pearls.
- 2) Each of the Parties shall ensure that the Pearl Coordinator(s) and Pearl Participants working in their institution have the powers they need to carry out the Pearls' tasks defined in this Regulation.
- 3) Follow-up of Pearl Participants at Parties shall take place as agreed between the sitting Pearl Participants and the Party of the departing Pearl Participant.
- 4) The String of Pearls Management shall handle the admission of new Parties.
- 5) The Pearl Coordinator may object for compelling reasons to the admission of a Pearl Participant in accordance with subsections 3 and 4 above on behalf of the Pearl which he/she represents. An objection pursuant to this subsection 5 shall be put before the String of Pearls Management.
- 6) Each Party shall make efforts to collect sufficient Donor Material and Donor Data to meet the objectives of the String of Pearls. Parties which exclusively collect Human Tissue for their Biobanks for more general research purposes shall ensure that they set aside sufficient Human Tissue to meet the objectives of the String of Pearls. The minimum quantity of Human Tissue per Donor that must be set aside for the String of Pearls must be defined in each Pearl-specific regulation. If it is not possible to define a minimum quantity, it must be specified what the initial quantity of Human Tissue per Donor should be.
- 7) Donor Material and Human Tissue earmarked for the objectives of the String of Pearls may not be used for purposes other than Research by or on behalf of the String of Pearls or the Pearl concerned.
- 8) Parties shall ensure that the Donor Material stored in the Biobank(s) managed by them is managed and registered with care. Parties shall furthermore ensure that the Donor Material satisfies the quality requirements formulated in the context of the String of Pearls, or in the absence thereof, the quality requirements generally applicable to the use of human tissue.
- 9) Each of the Parties shall be responsible for Disclosing the Donor Data and Donor Material to the Central Infrastructure.
- 10) A Pearl Participant can refuse to Disclose and/or Provide the Donor Data and/or Donor Material for a particular Research for compelling reasons. Refusal by a Pearl Participant must be notified in writing to the Pearl Coordinator by the management of the Party concerned, stating his/her reasons. The management of the Party with which the Pearl Coordinator is associated may lodge an objection to the Pearl Participant's refusal with the String of Pearls Management. Objections lodged with the String of Pearls Management are governed by the Procedure of the Disputes Committee. Pearl Participants are obliged to cooperate with the Disputes Committee in its handling of the objection. The final decision of the String of Pearls Management is binding.
- 11) Donor Data and Donor Material shall only be Provided by the Central Organisation on behalf of a Party after approval has been obtained for the Research as specified in Article 5 of this Regulation.

- 12) The Central Organisation shall ensure the prompt dispatch of sufficient relevant Donor Data for the Research and the requested quantity of Donor Material to the Party specified by the Pearl.
- 13) Parties may enter into joint ventures with third parties, including commercial parties, in the context of their collaboration within the String of Pearls. Collaboration within such joint ventures must meet the objectives and the underlying principles of the String of Pearls and this Regulation. Collaboration with third parties may be made subject to additional conditions to be defined by the String of Pearls Management, including with regard to valorisation. The conditions for collaboration with a third party must be defined in a written agreement between the parties.
- 14) An additional regulation shall be drawn up for each Pearl, describing the objectives of and defining the conditions for collaboration within the Pearl, along with the Pearl-specific conditions for collecting and using Human Tissue and Donor Data. These regulations must at least comply with the conditions described in this Framework Regulation.

## **5 Central Organisation**

- 1) The String of Pearls Board of Directors represents the String of Pearls to Parties and third parties. If it should be necessary for the functioning of the String of Pearls Initiative, the String of Pearls Board of Directors shall be authorised to enter into agreements with third parties, including but not restricted to the agreement referred to in Article 6, paragraph 6 of this Framework Regulation.
- 2) The String of Pearls Board of Directors shall form the Central Organisation in such a way that the current support requirements of the String of Pearls are met. The Central Organisation shall act under the direction and supervision of the String of Pearls Board of Directors.
- 3) The tasks handled by the Central Organisation shall include:
  - a) the drawing up of guidelines, specifications and SOPs to promote harmonisation in, among other things, the collection, storage and Pseudonymisation of Donor Data and Donor Material by Parties;
  - b) the formulation of policy and instructions for data security and the protection of privacy;
  - c) the provision of advice and support to departments and employees of Parties involved in the practical execution of the String of Pearls;
  - d) participation in European and international initiatives and committees on biobank activities with the aim of promoting supranational harmonisation and cooperation in the area of biobanks;
  - e) the collection and bringing together of Donor Data in the Central Infrastructure for the purpose of Provision;
  - f) informing potential Researchers about the availability of Donor Data and Donor Material for a particular Research study, either on their own initiative or at the request of the approached Pearl;
  - g) informing the Pearl Coordinators about requests to Disclose by potential Researchers;
  - h) the Provision of Donor Data and Donor Material to Researchers in such a way that the Donor Material and Donor Data of each individual Donor can be related to one other for each Donor by the Researcher; and
  - i) maintenance of an accurate record, accessible to Pearl Coordinators, of Donor Material and Donor Data provided for Research by a Pearl.
- 4) The Central Organisation is not permitted to make any undertakings on behalf of the Pearls and/or Parties regarding the actual Provision.
- 5) All the documentation referred to in Article 5.3 handled by the Central Organisation and/or working groups shall be made known to Parties and published on the String of Pearls website after adoption by the String of Pearls.

## 6 Protection of privacy

- 1) Parties shall ensure that the privacy of the Donor and the confidentiality of Donor Data are protected in accordance with the statutory requirements and codes of conduct applicable in the Netherlands to the use of Human Tissue and personal data, including in any event the *Personal Data Protection Act* and the *Code of Conduct: Proper Secondary use of Human Tissue*<sup>11</sup>.
- 2) Parties shall only Disclose Human Tissue and Donor Data to the Central Organisation in pseudonymised form. The Party under whose responsibility Human Tissue and Donor Data is collected, managed and Disclosed to the Central Infrastructure is furthermore responsible for Pseudonymisation in accordance with the guidelines and instructions issued by the Central Organisation, so that the Human Tissue and Donor Data:
  - a) can be effectively exchanged between Parties and used for Research in the context of the String of Pearls, and
  - b) cannot be traced back to an individual Donor by the Party that obtains it without disproportionate time and effort.
- 3) Prior to the Provision, the Donor Data shall be given a new Pseudonym by or on behalf of the Central Organisation.
- 4) The String of Pearls Board shall ensure that the Central Infrastructure and the information stored therein are adequately protected and that sufficient technical and other measures have been put in place to prevent unauthorised access to the Central Infrastructure and to prevent the loss, theft and unauthorised use of the Donor Data.
- 5) The String of Pearls Board of Directors may outsource the compilation and assignment of the Pseudonyms and the storage of the Central Infrastructure to a third party on behalf of Parties. This third party will then be a processor within the meaning of the Personal Data Protection Act.
- 6) If and to the extent that Pseudonymisation and storage and the management of the Central Infrastructure are outsourced to a third party, the String of Pearls Board of Directors shall enter into a written processor's agreement with such third party on behalf of Parties. The processor's agreement must at least define the requirements with which Pseudonymisation must comply, as well as the method to be used to ensure the security and confidentiality of the information contained in the Central Infrastructure, and what conditions will apply to the Disclosure and Provision of personal data and human tissue.
- 7) The String of Pearls Board of Directors shall inform Parties about the method of Pseudonymisation and the location of the Central Infrastructure (and any changes to the location), and, if applicable, shall also pass on the details of the third party performing the Pseudonymisation and managing the Central Infrastructure.
- 8) The Pearl regulations and the agreement with external Researchers shall contain a ban on coupling as referred to in the *Code of Conduct: Use of Data in Health Research*.

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<sup>11</sup> The Code of Conduct is published on the website of the Dutch Federation of Biomedical Scientific Societies: [www.federa.org](http://www.federa.org).

## **7 Review**

- 1) Regulations drawn up by the Pearls pursuant to Article 4, paragraph 15 above shall be submitted to the String of Pearls Board of Directors for approval.
- 2) The regulations approved by the String of Pearls Board of Directors shall be submitted to the MERC of the Party for which the Pearl Coordinator works together with the written information, informed consent forms and other relevant documents to be used by a Pearl. Regulations are in any event defined as: the document that describes the objectives, activities and procedure of a Pearl, and the agreement or regulation of the Scientific Committee referred to in paragraph 4.
- 3) Substantial amendments to the documents described in the previous paragraph must be submitted to the String of Pearls Board of Directors for approval and, if required, to the MERC for further approval.
- 4) A Scientific Committee shall be set up or appointed for each Pearl. The composition, powers and procedures of the Scientific Committees shall be described in more detail in an agreement or regulation agreed for each Pearl, the minimum requirements for which are defined in Annex III to this Regulation<sup>12</sup>.
- 5) Research may only be performed if consent has been obtained from a Scientific Committee on the basis of a sound research protocol. If required under prevailing legislation and regulations, prior positive recommendation or approval must have been obtained from an MERC. A research protocol may only be submitted to a Scientific Committee or an MERC once it has been approved by the Pearl concerned.
- 6) Without prejudice to Article 7, paragraph 5, the Scientific Committee or a Party may decide that a research protocol must be submitted to an approved MERC, or may seek advice from a MERC before making a decision.

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<sup>12</sup> This also includes the minimum requirements with which a research protocol must comply.

## 8 Conditions for use

- 1) Notwithstanding any other conditions relating to the collection, storage and use of Donor Data and Donor Material set out in this Framework Regulation, the provisions of this Article 8 shall apply to the use of Donor Data and Donor Material.
- 2) Donor Material and Donor Data may be used by a Party on behalf of the String of Pearls provided that:
  - a) they are obtained by a Party with the consent of the Donor in accordance with the requirements of Article 9, paragraphs 1-5; and
  - b) the other requirements of this Framework Regulation are met.
- 3) If Human Tissue not collected in the context of the String of Pearls is used for Research, such material may only be used for Research if it has been obtained and stored in a valid and ethical way. Residual material and associated medical data may be used for Research if obtained and stored by a Party in accordance with the Code of Conduct for the Use of Data in Health Research (*Gedragcode Goed Gebruik*) and the Code for Proper Secondary Use of Human Tissue *Gedragcode Goed Gedrag*) published by the Dutch Federation of Biomedical Scientific Societies.
- 4) Responsibility for compliance with the conditions in the previous paragraph lies with the Party that manages the Biobank from which the Human Tissue has been obtained, unless the Human Tissue has been obtained from a third party. In this case the conditions in the previous paragraph shall be set out in a written agreement.
- 5) Researchers shall be bound by the regulation of the Pearl Providing the Donor Material and the Donor Data. The applicable conditions must be made known to the Researcher prior to their Provision.
- 6) Human Tissue left over after Research by internal Researchers shall be returned to the Biobank(s) of the Parties from which the Researchers obtained the Human Tissue.
- 7) Where Research is partly or entirely carried out by an external Researcher, Parties shall ensure that a written agreement is entered into with the external Researcher in which the Donor's rights of control and privacy are safeguarded and which sets out disposal of any remaining Human Tissue after completion of the Research<sup>13</sup>.
- 8) The Pearl concerned is responsible for monitoring the return and/or destruction by the external Researcher of all Human Tissue Provided by the Pearl and remaining after completion of the Research by the external Researcher and shall if necessary take measures to ensure that this is done. The Pearl shall furthermore ensure that the Human Tissue is returned to the Biobank(s) from which it was obtained.
- 9) Provision and Research shall only take place if prior consent has been obtained in accordance with Article 7 of this Regulation.
- 10) The Pearl Providing the Donor Material and Donor Data shall ensure that no more Donor Material and Donor Data are provided than is strictly necessary for the Research.
- 11) Donor Material can only be Provided to an external Researcher without a Pearl being involved in the execution of the Research in exceptional cases.

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<sup>13</sup> A model agreement is appended hereto in Annex VI

- 12) If a Pearl ceases to exist, the Parties to which the Pearl belonged may, in consultation with the String of Pearls Board of Directors, continue to Provide the Donor Material. The provisions of the Regulation shall remain applicable to the Donor Material.

## **9 Donor's right of control**

- 1) This Regulation shall not apply to the use of residual material to which the provisions of the Code of Conduct for the Proper Secondary Use of Human Tissue apply.
- 2) Donor Material and Donor Data may only be obtained from a Donor for the purposes of the String of Pearls in accordance with the provisions of paragraphs 2 to 8 of this Article 9.
- 3) The Pearl Participants shall ensure that prior to giving his/her consent the Donor has been given sufficient information, in accordance with the requirements of the WMO, on the consequences, burdens and risks associated with the removal of the Human Tissue and the Provision of the Human Tissue and Donor Data in the context of the String of Pearls. If a Donor is unable to read, the information must be given to him/her verbally during the personal consultation.
- 4) The Donor shall be given sufficient time to enable him/her to make a carefully considered decision on the basis of the information provided.
- 5) The Donor must have given his/her written consent to the removal, storage and use of his/her Donor Material and Donor Data prior to his/her participation. The consent shall address the objective of the String of Pearls or a specific Pearl and the conditions under which they operate.
- 6) If a Donor is unable to write, consent may have been obtained in the presence of at least one witness appointed by the Donor.
- 7) A contact (person or department) shall be appointed by each Party, from whom/which a Donor can obtain advice on the consent he/she intends to give. The contact details of such a person or department shall be included in the information leaflet.
- 8) Wherever possible, removal of Donor Material shall take place during a treatment indicated for the Donor in the context of his/her patient care, during which the Donor Material can be obtained with minimal additional burden and risk for the Donor. If Donor Material can only be removed outside of the Donor's indicated care, this shall only take place with the consent of the Donor.
- 9) Donor Data shall only be collected from Donors in accordance with the String of Pearls Information Model defined separately for each Pearl. If additional Donor Data is collected for a particular Research, this shall only be done with the consent of the Donor.
- 10) The Donor may withdraw his/her consent partially or in full at any time, without penalty or explanation.
- 11) Once the consent has been withdrawn, no new Donor Material shall be removed from the Donor for the Biobank and no additional Donor Data shall be collected from the Donor and transferred to the Central Infrastructure.
- 12) Upon withdrawing his/her consent, the Donor may specify that any of his/her Donor Material that may be present in the Biobank of the Party with which he/she is a patient for the purposes of the String of Pearls and the Donor Data stored in the Central Infrastructure:
  - a) may be used in accordance with his/her consent given previously, either under the Pseudonym or completely anonymously, or

- b) must be destroyed, notwithstanding the provisions of paragraphs 13 and 14.
- 13) Donor Data that has been Provided for specific Research prior to the withdrawal of the consent shall remain available in the form in which it was Provided for the purposes of the Research and in accordance with the prevailing legislation and regulations.
  - 14) Unless it is stated in the written information pursuant to which the Donor previously gave his/her consent that Donor Material Provided for Research is not eligible for destruction, such Donor Material shall likewise be destroyed after withdrawal of the Donor's consent. In that case the Research agreements with external Researchers shall contain a provision which makes it possible to destroy or return the Donor Material.
  - 15) Withdrawal of consent shall not lead to destruction of Findings.
  - 16) The consent obtained during a Donor's lifetime and not withdrawn by him/her in the interim shall remain in force after his/her death.
  - 17) The information leaflet must inform the Donor of the opportunity to withdraw his/her consent and the consequences of doing so.

## **10 Additional conditions for minor Donors and Donors incapable of giving informed consent**

- 1) Donor Material and Donor Data from minors and adults incapable of giving informed consent may only be used for Research if the provisions of this Article 10 are met. Insofar as no supplementary provisions are imposed in this Article, the provisions of Article 9 shall remain applicable to minor Donors and Donors incapable of giving informed consent.
- 2) The use of Donor Material and Donor Data must be necessary to achieve the objective of the Pearl concerned or the Research, which cannot be achieved by the use of Donor Material and Donor Data from Donors capable of giving their informed consent.
- 3) The risks to the Donor must be negligible and the objections must be minimal.
- 4) In the case of minor Donors, written consent must have been obtained from:
  - a) the Representative of the minor who is below the age of 12;
  - b) the minor aged 12 or older, and their Representative.
- 5) In the case of a person below the age of 18 who is incapable of giving informed consent, written consent must have been obtained from the Representative of that Donor.
- 6) If the Donor incapable of giving informed consent is aged 18 or older, the consent of one of the following people must have been obtained: If and only if the first person is absent or will not or cannot make a decision on behalf of the adult incapable of giving informed consent, the next person on the list may give consent:
  - a) the legal representative;
  - b) the person authorised in writing by the person incapable of giving informed consent;
  - c) the spouse, registered partner or other life partner;
  - d) the parents;
  - e) reasonably accessible adult children; or
  - f) adult brothers or sisters.
- 7) The Treating Physician shall ensure that the minor Donor or the Donor incapable of giving informed consent is informed in a way that is appropriate to his/her intellectual capacity. The Treating Physician may delegate this to a person who is trained in the provision of information to this group of Donors.
- 8) If the Donor objects to the removal of particular Donor Material, that Material shall not be removed. The Codes of Conduct of the professional groups concerned shall be adhered to<sup>14</sup>.
- 9) If more tissue is likely to be removed after the Donor's 18th birthday or after his/her mental incapacity status ceases, the Donor shall be asked whether the consent given previously by him/her still accords with his/her wishes. The Donor shall sign the informed consent form again. If the Donor refuses to give his/her consent, the provisions of Article 9, paragraphs 10 to 15 shall apply accordingly.

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<sup>14</sup> The Codes of Conduct are published on the CCMO website: <http://ccmo.nl>

## **11 Information on research outcomes**

- 1) Findings of Research carried out by Internal Researchers shall be published in a manner that is customary for knowledge institutes or the professional group and shall at least be in accordance with the Statement on Publication Policy of the Central Committee on Research Involving Human Subjects<sup>15</sup>.
- 2) Findings from Research carried out by external Researchers must be published as agreed between the Pearl concerned and the external Researchers, based on the principles set out in the Statement on Publication Policy. This principal may only be deviated from in the event of urgent objections, as approved by the Pearl.
- 3) The Party on behalf of which the Donor Data and the Donor Material are Provided shall be informed by the Central Organisation about Serendipity Findings that have been notified to the Central Organisation. Each Party shall ensure that Serendipity Findings are reported in the correct manner in accordance with its own internal policy.
- 4) The agreements with the external Researcher shall specify that Findings as referred to in paragraphs 2 and 3 above obtained from Research by the external Researcher concerned shall be reported to the Pearl.
- 5) Donors shall under no circumstances be informed directly by the Researcher or the Pearl carrying out the Research unless the Researcher is also the Treating Physician.
- 6) Results may only be patented, licensed and/or commercialised on the basis of arrangements to be made between the Parties.

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<sup>15</sup> This statement can be found on the CCMO website under 'Memoranda and statements'.

## **12 Accountability to the String of Pearls Management**

- 1) The Pearl Coordinator shall ensure that the activities of the Pearl are reported to the String of Pearls Management on an annual basis. The reports must at least cover the following subjects:
  - a) the number of Donors added to the research database;
  - b) the quantity of Donor Material obtained and Provided for research and information on any remaining Donor Material;
  - c) the number of Donors who withdrew their consent;
  - d) the number of Research applications per year;
  - e) the number of Research projects carried out per year by or with the cooperation of the Pearl, divided into external and internal research;
  - f) monitoring of careful management and recording of medical information and biobank data;
  - g) any organisational problems;
  - h) income and expenses, if applicable.
- 2) The String of Pearls Management may decide that additional subjects should be reported.
- 3) The String of Pearls Management shall inform Parties in good time about:
  - a) the final list of subjects to be reported;
  - b) the format in which reports are to be issued;
  - c) the latest date by which reports must be received.

### **13 Donor complaints procedure**

Interested parties may submit complaints relating to or arising from Donorship in the context of the String of Pearls to the complaints committee of the Party at which the Donor is a patient and/or where the Donor Material and Donor Data were collected.

## **14 Objections and appeals**

- 1) Pearl Participants may lodge objections to the decisions of the Scientific Committee (see Article 5, paragraph 3) in accordance with the Procedure for the Working Method of the Scientific Committee.
- 2) The String of Pearls Management is exclusively authorised to deal with:
  - a. appeals against the decision of a Scientific Committee on an objection lodged against that Scientific Committee;
  - b. disputes arising from the Provision of Donor Material and Donor Data for Research;
  - c. disputes arising from the admission of Pearl Participants under Article 4, paragraph 5 of this Framework Regulation;
  - d. other matters affecting the progress of the String of Pearls.
- 3) There is a Disputes Committee with the tasks and powers defined in the Procedure of the Disputes Committee (Annex IV).
- 4) The String of Pearls Management may obtain advice from the Disputes Committee. The advice of the Disputes Committee must be sought for decisions by the String of Pearls Management pursuant to Article 12, paragraph 2 a.
- 5) The decision of the String of Pearls Management is binding.

## **15 About this document**

- 1) This Regulation may be referred to as follows:  
*String of Pearls Initiative: Framework regulation for the collection, storage and use of human tissue for medical research. Amsterdam, 2008*
- 2) Copyright is vested in the String of Pearls Initiative (PSI).