HORIZON-MISS-2023-CANCER-01-01

GLIOMATCH

Project No. 101136670

The malignant Glioma immuno-oncology matchmaker: towards data-driven precision medicine using spatially resolved radio-multiomics

Deliverable 5.2

Legal definition of sample and data sharing of the multicentric clinical trial design

WP 5 – Implementation of clinical trial for proof-of-concept
Version 1.0

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Delivery date	04 June 2024
Dissemination level	PU = Public
Type	R = Document, report

Funded by the European Union

Funded by the European Union. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or the European Health and Digital Executive Agency (HaDEA). Neither the European Union nor the granting authority can be held responsible for them.

UKRI Innovate UK

This work is supported by Innovate UK [grant number 10113516].
This work has received funding from the Swiss State Secretariat for Education, Research and Innovation (SERI).

Revision history

Author(s)	Description	Date
Rüdiger Sorg (UDUS), Anubhuti Sinha (Timelex) and Jos Dumortier (Timelex)	Deliverable draft	22 May 2024
Judith Verhagen-Oldenampsen (EMC) and Einar Vik-Mo (OUS)	Revision 1	31 May 2024
Rüdiger Sorg (UDUS), Anubhuti Sinha (Timelex)	Revision 2	03 June 2024
Eva Avilla Royo (accelCH)	Formatting and formal check	04 June 2024

Contents

Partner short names

Short name	Partner
KUL	Katholieke Universiteit Leuven
EMC	Erasmus Universitair Medisch Centrum Rotterdam
UM	Universiteit Maastricht
OUS	Oslo Universitetssykehus HF
UDUS	Heinrich-Heine Universität Düsseldorf
AA	Aspect Analytics NV
Timelex	Timelex BV/SRL
accelCH	accelopment Schweiz AG

Abbreviations

Abbreviation	Term
CTR	Clinical Trial Regulation. Regulation 536/2014 of the of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, as maybe amended from time to time.
CA	Consortium Agreement
D	Deliverable
DC	Dendritic cell
DCVax	Dendritic cell vaccination
GA	Grant Agreement
GBM	Glioblastoma
GDPR	General Data Protection Regulation. Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016 on protection of natural persons with regard to the processing of personal data and on the free movement of such data, repealing Directive 95/46/EC, as maybe amended from time to time.
HEU	Horizon Europe
M	Month
WP	Work Package

Executive summary

This deliverable describes some of the initial legal principles which will be followed while conducting the clinical trials in the GLIOMATCH project. The Clinical Partners in the consortium who will oversee these clinical trials will have to design a legally compliant study protocol along with informed consents for their respective ethics committee and relevant regulatory authorities.

UDUS, EMC, FINCB, KUL and OUS are conducting different therapeutic strategies and will be responsible for their respective obligations regarding sponsorship, study protocols, investigators' brochures, etc. All five clinical partners are part of the Consortium and have executed the Grant Agreement. Thus, they are all joint controllers in accordance with the EU General Data Protection Regulation (GDPR). UDUS, EMC, FINCB, KUL and OUS will be part of the joint controller arrangement that describes their roles and responsibilities in order to comply with Art. 26 of the GDPR.

Further, the study protocol, informed consent and other relevant documents shared with the subjects for the GLIOMATCH project will also describe the joint-controller arrangement and provide details of the processing of personal data taking place by each of the Consortium Partners forming a part of the GLIOMATCH project.

The next steps include framing the clinical trial protocols and informed consent framework along with preparing relevant legal documents such as the joint controller arrangement and/or material transfer agreements to fulfil the obligations under the GDPR and Clinical Trial Regulation (CTR). Further, the legal framework will be described in detail in the deliverables connecting with the current deliverable 5.2 as described in section 3 below.

1 Introduction

The GLIOMATCH project is a Research and Innovation Action funded by the European Union under Horizon Europe. The project will develop and implement a treatment selection platform that allows clinicians to better match immunotherapy treatments for adult glioblastoma (GBM) and paediatric high-grade glioma patients. The GLIOMATCH project started in January 2024 and will last 5 years.

In WP5 of the GLIOMATCH project, 'Implementation of clinical trial for proof-of-concept', the partners UDUS, KUL, FINCB, OUS and EMC will conduct five small-scale, explorative, prospective immunotherapy trials on adult glioblastoma patients, combining dendritic cell (DC) vaccination (DCVax) targeting personalised tumour antigens (autologous whole tumour lysates/tumour stem cell + survivin/TERT mRNA) with strategies tackling factors, which have been identified to affect efficacy (conducted by UDUS, KUL, FINCB, OUS), or Oncolytic Virus Therapy (OVT) using Newcastle Disease Virus (NDV; conducted by EMC). Thereby, the effect of different factors and different immunotherapeutic approaches can be addressed in parallel, while collecting unique tumour tissue from primary and recurrent tumours as well as tumours at 2nd recurrence after immuno-therapy for spatial radio-multiomics studies and analyses of associations between clinical and immunological outcomes in the respective trial and the results from radio-multiomics analyses.

This deliverable D5.2 provides an overview of the legal definition of the sample and data sharing of the multicentric clinical trial design. Certain aspects of this deliverable will be detailed in subsequent deliverables referred to in Section 3 of this document.

2 Legal framework governing the clinical trials

2.1 General Data Protection Regulation

2.1.1 Important definitions under the GDPR

Personal data

The General Data Protection Regulation (GDPR) comes into play in situations where there is processing of personal data, whether wholly or partly by automated means. Article 4(1) defines "personal data" as any information relating to an identified or identifiable natural person *directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.* 'Any information' can be interpreted broadly to include 'private' information as well as publicly known information.[1] It can be objective information, such as a name, date or place of birth, profession, etc. but also subjective information, such as an opinion expressed by someone or an evaluation or assessment relating to a person. For example, in the Nowak case, the CJEU ruled that 'the expression "*any information' […] reflects the aim of the EU legislature to assign a wide scope to [the concept of personal data], which is not restricted to information that is sensitive or private, but potentially encompasses all kinds of information, not only objective but also subjective, in the form of opinions and assessments*".[2]

Therefore, the concept of "personal data" includes any kind of information, irrespective of its form, alphabetical, numerical, graphical or acoustic. It can consequently be textual information, structured in the form of records in a database but also unstructured, for example in a report or an e-mail. But it can also consist of a picture, a drawing, a voice mail or a video.

Further, to be characterised as "personal data", the information must concern an identified or identifiable person. Recital 26 specifies this condition as follows: "*To determine whether a 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 any other person to identify the individual directly or indirectly. To ascertain whether means are reasonably*

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[1] Judgment of the European Court of Justice C-101/2001of 6.11.2003 (Lindqvist), §24: 'The term undoubtedly covers the name of a person in conjunction with his telephone coordinates or information about his working conditions or hobbies.

[2] CJEU, Case C-434/16, Judgment of 20 December 2017, Peter Nowak v. Data Protection Commissioner, ECLI:EU:C:2017:994, https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX:62016CJ0434.

likely to be used to identify the individual, account should be taken of all objective factors, such as the costs of and the amount of time required for identification, taking into consideration both available technology at the time of the processing and technological development."

Recital 26 of the GDPR further states: "*To ascertain whether means are reasonably likely to be used to identify the natural person, 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*."

It may also be noted that personal data refers to identified or identifiable data of *natural persons* i.e. GDPR is applicable only when the processing is in relation to personal data of a natural person. However, the GDPR does not apply to deceased persons as the protection of personal data is considered a non-transmissible personal right which extinguishes by the death of the data subject.

The clinical trials will engage patients in 5 clinical sites based on the criteria described in D5.1 and will administer different type of immunotherapies and study their impact. The clinical trials under WP5 also propose to collect GBM tissue samples for spatial multiomics and will be correlated with relevant MRI images for radio-multiomics for the GLIOMATCH project.

Genetic Data and Health Data

The GLIOMATCH project will primarily work with health information and tissue samples. The GDPR specifically defines both in order to establish clear conditions for the processing of such personal data. According to Article 4(13) of the GDPR, "genetic data" is defined as personal data relating to *inherited or acquired genetic characteristics of a natural person providing unique information about the physiology or health of that natural person from an analysis of a biological sample from such a natural person*. Recital 34 of the GDPR further stipulates that '*genetic data particularly includes chromosomal, DNA and RNA analysis or from another element enabling equivalent to be obtained*.'

Genetic data are closely related to "health data". Under the GDPR, "*personal data concerning health should include all data pertaining to the health status of a data subject which reveal information relating to the past, current or future physical or mental health status of the data subject. This includes information about the natural person collected in the course of the registration for, or the provision of, health care services to that natural person; a number, symbol or particular assigned to a natural person to uniquely identify the natural person for health purposes; information derived from the testing or examination of a body part or bodily substance, including from genetic data and biological samples; and any information on, for example, a disease, disability, disease risk, medical history, clinical treatment or the physiological or biomedical state of the data subject independent of its source, for example from a physician or other health professional, a hospital, a medical device or an in vitro diagnostic*".

Health data and genetic data belong to the category of 'special' personal data. Because of its sensitive nature such data is subject to stricter rules than 'common' personal data such as names, addresses, telephone numbers, etc. Therefore, when processing health and genetic data, a controller is required to comply with Article 9 of the GDPR along with Article 6 of the GDPR when deciding on the purpose of the processing.

Processing

Under Article 4(2) of the GDPR, "processing" involves any operation performed on personal data, including collecting, accessing or storing personal data. Accordingly, the definition of processing is fairly broad under the GDPR and encompasses nearly all uses of personal data, including situations where personal data is collected to create a repository, where artificial intelligence (AI) is trained on personal data, or where AI is utilised to analyse and make decisions about individuals.

Controllers, Joint Controllers and Processors

Under the GDPR a controller determines the means and purposes of the processing activities i.e. the ‘how’ and ‘why’ of data processing. A controller can be a natural or legal person, public authority, agency or other body.[3]

According to Art. 4(7) of the GDPR, a controller may individually or jointly determine the means and purposes of the data processing. In the event where two or more controllers jointly determine the means and purposes of data processing, then the obligation under Art. 26 of the GDPR is required to be complied with. Art. 26 of the GDPR requires all controllers to have a joint controller arrangement describing the roles and responsibilities of each controller.[4] This is to ensure that each controller fulfils their respective transparency obligation to the data subjects.

On the other hand, a natural or legal person, public authority, agency or another body will be considered to be a “processor” if:

a. it is separate from the controller; and
b. it processes personal data on behalf of the controller.[5]

Typically, the controller and the processor are required to execute an agreement describing the roles and responsibilities of the processor. A data processing agreement usually covers the following:

a. the subject matter and duration of the processing;
b. the nature and purpose of the processing;
c. the type of personal data and categories of data subjects;
d. the rights and obligations of the controller and processor including the understanding that the processing by the processor will only be in accordance with the controller’s instructions;
e. conditions for the processor to engage another processor;
f. confidentiality requirements and appropriate security measures to be implemented and adhered to by the processor;
g. the requirement to delete or return all personal data to the controller at the end of the processing service;
h. the requirement to produce information necessary to demonstrate compliance and contribute to audits and inspections carried out by the controller; and
i. obligations on the processor to assist the controller in fulfilling its responsibilities.

The GLIOMATCH project is a research project under Horizon Europe where all consortium partners have participated in the execution of the Grant Agreement and Consortium agreement. To maintain their transparency obligations, the partners will enter into a joint-controller arrangement. The joint controller arrangement will describe the roles and responsibilities of each partner and also provide for a data breach notice in accordance with the GDPR.

Consent

Recital 32 of the GDPR states that consent should be given by a *clear affirmative* act establishing a *freely given, specific, informed and unambiguous* indication of the data subject’s agreement to the processing of personal data. Consent is one of the six lawful bases provided under Art. 6 of the GDPR. According to Art. 4(11) of the GDPR, the consent of a data subject must fulfil the following the elements:

- freely given i.e., the real choice and control of the data subjects,
- specific i.e., ensuring there is purpose specification, granularity in consent requests and clear separation of information related to obtaining consent for data processing activities.
- informed i.e. the data subject is informed of important elements like details of the controller, purpose of each processing operation etc., and

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[3] Article 4(7) of the GDPR.
[4] Article 26 of the GDPR.
[5] Article 4(8) of the GDPR.

- unambiguous indication of the data subject's wishes by which he or she, by a statement or by a clear affirmative action, signifies agreement to the processing of personal data relating to him or her.[6]

The consent under the GDPR is slightly different from the informed consent required under the Clinical Trial Regulation. Under the GDPR, for processing health and genetic data an explicit consent is required. Therefore, subject to the applicable national laws and regulations, the informed consent for each of the clinical sites should include an explicit consent about the processing of personal data collected during the clinical trials. The informed consent should indicate that the partners are joint-controllers for the GLIOMATCH Project and describe the processing activities carried out by each partner including details of the personal data that may be transferred to the data lake.

2.1.2 General principles of data protection

Art. 5 of the GDPR lays down the general principles of data protection which are required to be followed by controllers. These are described briefly in this section. These principles will be analysed in detail in D1.3 (Legal requirements analysis for data and sample sharing within and beyond the consortium) due in M12.

a. *Lawfulness, Fairness and Transparency*

Lawfulness

The processing of any personal data requires a lawful purpose as elaborated in Art. 6 of the GDPR. Furthermore if special category data is being processed, a controller is required to also comply with Art. 9 of the GDPR. One of the legal bases provided under Art. 6 is 'consent' (as defined hereinabove). Art. 7 of the GDPR elaborates on the conditions of consent as follows: (i) the controller is required to demonstrate that the data subject has consented to the processing of their personal data; (ii) the consent can be a written declaration that is in an intelligible and easily accessible form, using clear and plain language; and (iii) the data subject should be informed of their right to withdraw their consent and the process entailed to follow such withdrawal of consent.

Article 9(2)(a) requires 'explicit' consent to be obtained from the data subjects. The usage of the term 'explicit' refers to the data subjects giving an express statement of consent, which is unequivocal and does not leave room for any doubt.[7] The clinical trials will also collect special category data; therefore the consent will have to be 'explicit'.

Fairness and Transparency

This principle requires the data subjects to be informed about the processing of their personal data and obliges the controller to describe the essential elements of processing , such as the identity of the controller, the purpose of processing, the information being processed, the various categories of personal data being processed, the period of storage, the risks, rules, safeguards, and rights of data subjects in relation to the processing.

b. *Purpose Limitation*

Art. 5(1)(b) covers the principle of purpose limitation which requires the data subject to be clearly and specifically informed of each of the processing activities proposed. This principle aims to reduce further processing of personal data.

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[6] EDPB Guidelines 05/2020 on consent under Regulation 2016/679, version 1.1, https://edpb.europa.eu/sites/default/files/files/file1/edpb_guidelines_202005_consent_en.pdf

[7] EDPB Guidelines 05/2020 on consent under Regulation 2016/679, version 1.1, https://edpb.europa.eu/sites/default/files/files/file1/edpb_guidelines_202005_consent_en.pdf

The purposes for processing of data will also be covered in the informed consent. The following purposes will be included in addition to the main purpose for conducting the clinical trial:

- For further scientific research purposes. This includes publication and dissemination activities (e.g., disclosure of the methods and results of the study through presentation at reputable scientific symposia and professional meetings as well as through reputable scientific journals, theses, or dissertations). This may also potentially include the reuse of data subject’s data within the framework of a new research project related to the development of the GLIOMATCH platform, or research not related to GLIOMATCH but related to diseases, especially related to brain tumours.
- To additionally process the personal data as required by national or EU law.

c. *Storage Limitation*

The storage limitation principle requires personal data to be kept in a form which permits identification of data subjects for no longer than is necessary for the purposes for which the personal data are processed. This principle essentially requires the data controller to clearly state, prior to the processing, how long the personal data must be stored for to achieve the purposes of the processing.[8]

The clinical trial protocols and the informed consent will require to provide information on how long the personal data will be stored. This is usually in accordance with the applicable national laws.

d. *Accuracy Principle*

According to Article 5(1)(d) personal data shall be "*accurate and, where necessary, kept up to date; every reasonable step must be taken to ensure that personal data that are inaccurate, having regard to the purposes for which they are processed, are erased or rectified without delay*."[9] The principle of accuracy is strongly associated with the quality of data and is vital in guaranteeing the reliability and trustworthiness of personal data, which in turn is crucial for protecting the privacy rights of individuals.

e. *Data Minimisation*

According to Article 5(1)(c) of the GDPR personal data must be “*adequate, relevant and limited to what is necessary in relation to the purposes for which they are processed*”.[10] This principle goes hand in hand with the purpose limitation principle.

The clinical trial protocols and the informed consent will clearly identify the purposes for which the data will be processed and what type of personal data will be stored. The Clinical partners will identify the parameters of data that will be processed necessary for the success of the GLIOMATCH project.

f. *Integrity and Confidentiality*

Personal data must be protected by appropriate technical and organisational measures to ensure confidentiality, integrity, and availability in accordance with Article 32 of the GDPR. Technical and organisational measures can include a security layer implemented in an information system; which is dedicated to enhancing data protection within the system and managing data access through identity and access management protocols.

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[8] Article 5(1)(e) of the GDPR.
[9] Article 5(1)(d) of the GDPR.
[10] Article 5(1)(c) of the GDPR.

The clinical and technical partners will have a set procedure in place to adhere with this principle.

g. *Accountability Principle*
The accountability principle is featured in Article 5(2) of the GDPR. This principle requires the controller to take responsibility for and demonstrate compliance with the other six principles i.e., principles of: (i) lawfulness, fairness, and transparency, (ii) purpose limitation, (iii) data minimisation, (iv)storage limitation, (v) accuracy, and (vi) confidentiality and integrity.

Subject to the applicable national laws and regulations, the data protection notice included in the informed consent describes the role of each consortium partner and identifies them as the joint controllers. Details of each consortium partner is provided to the patient participating in the study in the patient information sheet. The consortium partners will enter into joint controllers' arrangement pursuant to Art. 26 of the GDPR. This is also connected with the transparency obligations of each of the partners.

2.1.3 Data subject rights

The GDPR provides the following rights to data subjects:

a. Right to information (Article 12 of the GDPR);
b. Right of access (Article 15 of the GDPR);
c. Right to rectification (Article 16 of the GDPR);
d. Right to erasure (Article 17 of the GDPR);
e. Right to restriction of processing (Article 18 of the GDPR);
f. Right to data portability (Article 20 of the GDPR);
g. Right to object (Article 21 of the GDPR);
h. Right not to be subjected to automated decision-making (Article 22 of the GDPR).

Subject to the applicable national laws and regulations, the data protection notice included in the informed consent should include details of the rights provided to the data subjects under the GDPR and elaborate if there are any modifications or limitations to such rights.

2.2 Clinical Trial Regulation

Each of the clinical partners conducting clinical trials will also have to adhere to the Clinical Trial Regulation (**CTR**) during the course of the trials. The CTR defines clinical trials as "*a clinical study that fulfils the following conditions: (a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned; (b) the decision to prescribe the investigational medicinal products is taken together with decision to include the subject in the clinical study; or (c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects*".

The GLIOMATCH project proposes to conduct 5 clinical trials in the following institutions relating to five different therapeutic strategies:

(i) **UDUS**: Vaccination with autologous tumour lysate-loaded DC in combination with the anti-PD-L1 anti-body Atezolizumab (2 groups, DC Vax / DC-Vax + anti-PD-L1, 3 patients each group);
(ii) **KUL**: Vaccination with autologous tumour lysate-loaded DC in combination with siRNA specific for Galec-tin-1 (3 groups, anti-Gal-1 / DC Vax / anti-Gal-1 + DC Vax, 3 patients each group);
(iii) **OUS**: Vaccination with autologous cancer stem cell, surviving and TERT mRNA transfected DC in combination with the anti-PD-L1 antibody Atezolizumab (2 groups, 3 patients each);
(iv) **FINCB**: Vaccination with autologous tumour lysate-loaded DC in combination with Tetanus toxoid preconditioning of the vaccination site (1 group, 6 patients);
(v) **EMC**: Oncolytic virus therapy using Newcastle disease virus (3 dose escalation groups with 3 allocated patients each and a one-off 3 additional patients in case of a dose-limiting toxicity, 1

expansion group at maximum tolerated dose with 10 allocated patients; in total a maximum of ~22 patients).

The legal framework applicable to the clinical trials will be described in D1.3 (Legal requirements analysis for data and sample sharing within and beyond the consortium) due in M12 of the project and D1.6 (Material and data transfer agreements) due in M18 of the project. This section introduces the important concepts that must be followed while designing the multicentric clinical trial design.

2.2.1 Overview of key requirements

The CTR requires that prior to authorisation of the clinical trial a unique identification number is created for the trial. Each partner is required to prepare the documents for its own clinical trial in compliance with the CTR and the applicable national laws of each of the sites. Key requirements such as preparing the study protocol, investigators' brochure, format of the informed consent, sponsorship of each of the clinical trials and insurance relating to the clinical trials will have to complied with all applicable regulations and guidelines.[11]

It may be noted that the Clinical Partners conducting the clinical trials will be considered as joint controllers for the GLIOMATCH project. As mentioned in section 2.1, the joint controller arrangement will describe the roles and responsibilities of all joint controllers.

2.2.2 Informed consent

The CTR requires each clinical site to obtain the informed consent of each of the subjects prior to their enrolment in the trial. Article 29 of the CTR outlines the requirements for informed consent that must be adhered to. According to Art. 29 of the CTR, an interview is required to take place with the subject, where the details of the clinical trial are clearly and comprehensively explained in lay person terms. The subject will be verbally informed about the trial by one of the investigators and provided with the patient information leaflet and informed consent form. The informed consent must also, amongst other things, clearly describe the following:

(i) nature, objectives, benefits, implications, risks and inconveniences of the clinical trial,
(ii) subject's rights and guarantees regarding his or her protection, in particular his or her right to refuse to participate and the right to withdraw from the clinical trial at any time without any resulting detriment and without having to provide any justification,
(iii) conditions under which the clinical trial is to be conducted, including the expected duration of the subject's participation in the clinical trial,
(iv) possible treatment alternatives, including the follow-up measures if the participation of the subject in the clinical trial is discontinued,
(v) include information about the applicable damage compensation system referred to in Article 76(1) of the CTR,
(vi) include the EU trial number and information about the availability of the clinical trial results in accordance with the CTR.

3 Future work

This deliverable is directly related to the following deliverables mentioned in WP1 'Data management and governance': D1.3 'Legal requirements analysis for data and sample sharing within and beyond the consortium' due in M12 and D1.6 'Material and data transfer agreements' due in M18.

4 References

1. European Data Protection Board's Guidelines 05/2020 on Consent under the GDPR. Accessible at: https://edpb.europa.eu/our-work-tools/our-documents/guidelines/guidelines-052020-consent-under-regulation-2016679_en.
2. The glossary section for 'data minimisation' on the website of the European Data Protection Supervisor. Accessible at: https://edps.europa.eu/data-protection/data-protection/glossary/d_en.

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[11] Clinical Trial Regulation.

3. Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016 on protection of natural persons with regard to the processing of personal data and on the free movement of such data, repealing Directive 95/46/EC.
4. Judgment of the European Court of Justice C-101/2001of 6.11.2003 (Lindqvist).
5. Case C-434/16, Judgment of 20 December 2017, Peter Nowak v. Data Protection Commissioner, ECLI:EU:C:2017:994, https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX:62016CJ0434.
6. Regulation 536/2014 of the of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.