Medicinal Products for Human Use - SWEDEN

Competent authority

Contact Details	**Contact Name 1** Medical Products Agency MPA - Läkemedelsverket **Contact Name 2** Department of Clinical Trials **Phone** +46 (0) 18 17 46 00 **Fax** +46 (0) 18 54 85 66 **Email Department** registrator@mpa.se **Address** P.O. Box 26 **ZIP/City** 751 03 UPPSALA **Country** Sweden (SE) **Web address** http://www.lakemedelsverket.se
Trial Authorisation / Registration / Notification	**Regulatory and ethics bodies involved in approval process** Competent Authority/-ies (CA) Ethics committee(s) Other **CA - Submission for authorisation mandatory for** Interventional IMP trials **CA - Registration/ notification without approval required for** – **CA - Submission required to** National CA Other **Specific Competent Authority for ATMP trials in place** Yes

	Competent Authority for ATMP trials Swedish Gene Technology Authorities (the Authorities responsible for the regulations of activities involving GMOs) In addition to MPA approval, a notification or application for permit might be necessary to be submitted to the Swedish Work Environment Authority SWEA (LVFS 2004:10). The rules are specified in SWEA Provisions (AFS 2011:2) on contained use of genetically modified micro-organisms. **Additional Information** Non-interventional studies (e.g. Epidemiological studies following AE on the market) will only be assessed by EC, not CA. Interventional studies will be judged by both CA and EC If ionising radiation is used the following authority shall be additionally involved: Swedish Radiation Safety Authority
Submission of Application	**Responsible for study submission** Sponsor **Entitled to study submission** – **Prerequisites for submission** – **Guidance on submission of application** The application procedure is specified on the MPA website in section “Electronic submission” or "Practical Guidance for submission" For further information please contact: registrator@mpa.se or eSubmission@mpa.se **Applicable national legal framework/ Reference** Chapter 4 LVFS 2003:6 (en) in LVFS 2006:1 (application procedure) SFS 2002:1086 (pursuant to Chapter 4 (4) LVFS 2003:6_en): Additional requirements as regards documentation on clinical trials with GMOs
Submission Format	**Format option(s)** Electronically **Preferred format** – **Guidance on submission format available** Yes **Guidance on submission format** The application procedure (e.g. required documents, EudraCT number)is specified on the MPA website in section “Electronic submission” or "Practical Guidance for submissions". For further information please contact: registrator@mpa.se or eSubmission@mpa.se
Language of Submission	**Language(s) of application** Swedish English **Preferred language of application** –

	English accepted Yes **Documents mandatory to be in official national language** Information material, Documents and Forms intended for study participants and patient information
Submission Fees	**Fees for trial submission mandatory** Yes **Fees** Application fee for authorisation to conduct clinical trials: 45.000 SEK (~ € 5.000) **Waiver for academic (non-commercial) studies possible** Yes **Official guidance on required fees** Payment requirements and unofficial English version of the applicable Ordinance (SFS 2010:1167) concerning fees are available on MPA website > Medicinal Products > Fees. **Applicable national legal framework/ Reference** Source: SFS 2010:1167 Ordinance concerning fees for the governmental control of medicinal products
Timelines Authorisation	**General timespan (max nr days)** 60 **Mode of approval (General)** Tacit (Silent) **ATMP/GMO trials (max nr days)** 90 **Mode of approval (ATMP/GMO trials)** Explicit **External expert advice required (max nr days)** 180 **Xenogeneic cell therapy (max nr days)** No time limit **Mode of approval (Xenogeneic cell therapy)** Explicit **Timespan counted from** Confirmation of formal completeness **Applicable national legal framework/ Reference** Chapter 5 (2) LVFS 2003:6 Chapter 5 (4-5) LVFS 2003:6

	Additional Information In case of any deficiencies in the application, the sponsor is granted one opportunity to submit supplementary information within 30 days. Explicit approval must also be obtained for clinical trials on active ingredients or components that are biological products of human or animal origin.
Amendments/ Substantial Amendments (SA)	**Notification mandatory for** Amendments which require a favourable opinion by the EC only **Authorisation mandatory for** Any substantial amendments **Responsible for submission of SA** Sponsor **Timeline for approval of SA (max nr days)** 35 **Guidance on submission of SA** A request for authorization (including the reasons for the amendments) shall be submitted electronically as indicated on the MPA website in section: Medicinal Products > Practical guidance for submissions **Applicable national legal framework/ Reference** Chapter 6 (1&2) LVFS 2003:6
Safety Reporting	**Responsible for AE reporting to CA** Sponsor **Sponsor must declare reportable events to** National CA CA(s) of EU&EFTA Member States concerned Relevant EC(s) All investigators **Reportable AEs** SAE (Serious Adverse Event) SUSAR (Suspected Unexpected Serious Adverse Reaction) **SUSAR being life-thereatening or leading to death must be reported** Within a max of 7d upon first knowledge (+ 8d for additional information) **All other SUSARs** Within a max of 15d upon first knowledge **SAE /SADE must be reported** – **National standard reporting form available** – **Reporting format - Options** – **Preferred format** – **Provision of Annual safety report mandatory** Yes

	Annual safety report shall be provided by sponsor to National CA Relevant EC(s) **Applicable national legal framework/ Reference** Chapter 6 (11-18) LVFS 2003:6) **Additional Information** In case of acute danger or risk to the study participants, the sponsor is obliged to inform the CA and the EC without delay of the measure taken (Chapter 6 (4) LVFS 2003:6) **Investigator shall report SAE to** – **Reporting timeline** –
End of Trial	**End of trial declaration mandatory for** All clinical trials requiring authorisation by CA **Responsible for End of trial declaration** Sponsor **Regular Termination - Declaration timespan (max nr days)** 90 **Timespan counted from** – **Early/premature Termination - Declaration timespan (max nr days)** 15 **Reasons for early termination shall be clearly stated** Yes **Applicable national legal framework/ Reference** Chapter 6 (7) & 7 (1-2) LVFS 2003:6 **Additional Information** Premature termination: reasons for the decision and the consequences for the trial participants must be clearly indicated.
Additional Information & Specifics	**Additional Information** The only CA for IMPs and MDs is the Medical Products Agency (MPA). Whether clinical trials with tissue or cell therapy will require a submission to the CA depends on the degree of manipulation and on the commercial potential of the “product”. A technique being offered by a specialist clinic provided at a certain hospital may be regulated by the National Board of Health and Welfare only (transplantation). If the technique or procedure is likely to be marketed, it will be regulated by the MPA and requires approval like a medicinal product. There is an option to create a system within the hospital for a specific patient, or for a group of patients, e.g. a new machine for renal dialysis. It is assumed that this is not research, but within the hospital clinical practise (a sort of “named patient basis”).

Ethics committee

Contact Details	**Contact Name 1** Central Ethical Review Board/ Centrala Etikprövningsnämnden (EPN) **Contact Name 2** c/o Vetenskapsrådet **Address** Box 1035 **ZIP/City** 101 38 Stockholm **Country** Sweden (SE) **E-Mail** kansli@cepn.se **Web address** http://www.epn.se **Additional Information** Responsibility: Supervision, Appeals
Ethical Review – General	**Submission for Ethical review mandatory for** All research projects involving humans **Submission to CA and EC to be performed in the following order** In parallel Sequentially (in any order) **Additional Information** In Sweden, all research involving humans or their integrity must be reviewed by the Ethical Review board(s). Non-interventional studies (e.g. Epidemiological studies following AE on the market) will only be assessed by EC, not CA. Interventional studies will be judged by both CA and EC NB! If ionising radiation or radiological methods are used: Additional approval from Local Radiation Protection Committees (at university hospitals) is required! **Regulatory and ethics bodies involved in approval process** –
Single-Centre Studies - Ethical Review	**Ethical approval (favourable opinion) to be obtained from** Regional EC competent for the study site resp. health facility **Additional Information** The competent Regional Ethical Review Board of the catchment area of the trial site is responsible for evaluation of the single-centre study. Appeals against regional EC’s decisions can be submitted to the Central EC (pursuant to Section 36 2003:460).
Multi-Centre Studies - Ethical Review	**Ethical approval (favourable opinion) required from** Lead EC (authorised to issue a single opinion) **Submission of application required to** Lead EC + All concerned local ECs for site-specific assessment

Additional Information

There are 6 Regional Ethical Review Boards in Sweden who are authorized to issue a (single) vote in mono- and multi-centre trials (according to Chapter 5 (7) LVFS 2003:6).

The favourable single opinion shall be requested from the geographically relevant Regional Ethical Review Board depending where the responsible research body/ Principal Investigator is located. If a responsible research body is located in a country other than Sweden, or if its location is undetermined, the application is to be submitted to the board in whose catchment area most of the research is to be conducted.
The geographically defined catchment areas for the Regional ECs are listed in Annex 1 of 2003:615.

The EC's review of the application includes an assessment for each trial site of the PI's qualification and the suitability of the trial site (Chapter 4 (6) LVFS 2003:6).

Appeals against regional EC's decisions can be submitted to the Central EC (pursuant to Section 36 2003:460).

Submission of Application

Responsible for study submission

Sponsor

Entitled to study submission

–

Prerequisites for submission / approval

–

Guidance on study submission

Various guidance documents on application procedure, research plan, information for trial subjects as well as the English version of the application form are available in English on the Central EC website in Section Application.

Additional Information

An application is deemed complete when the application form has been filled in correctly, the required appendices are attached and the fee has been paid.

The sponsor ensures that a copy of the EC's opinion is submitted to the MPA within 15 days after receipt.

NB! If ionising radiation or radiological methods are used:
Additional approval from Local Radiation Protection Committees is required!

Submission Format

Format option(s)

–

Preferred format

–

Standard application form available

Yes

Standard application form

"Ansökningsblanketten" (.doc)
The standard application form for submission to all regional boards is available on the Central EC website in section Application.
CAVE: Only the Swedish form is accepted!

Guidance on submission format

A guide to the application is available on the Central EC website in section Application.

Language of Submission	**Language(s) of application** Swedish **Preferred language of application** – **English accepted** The annex for professional experts (research plan, protocol) may be written in English. **Documents mandatory to be in official national language** –
Submission Fees	**Fees for Ethical review mandatory** Yes **Fees for Ethical review** Fees range from 2,000 SEK (approx. 220€) for an amendment to 16,000 SEK (approx. 1,760€) for pharmaceutical trials, or multi-centre studies. **Official guidance on required fees** The detailed fees are provided in the Application form (Ansökningsblanketten) available on the EPN website resp. in Annex 2 of 2003:615. **Applicable national legal framework/ Reference** Annex 2 of 2003:615
Timelines Ethical Review	**General timespan for single-centre studies (max nr days)** 60 **General timespan for multi-centre studies (max nr days)** 60 **ATMP/GMO trials (max nr days)** 90 **External expert advice required: Timespan (max nr days)** + 90 **Xenogeneic cell therapy: Timespan (max nr days)** No time limit **Timespan counted from** Date of submission of valid application **Applicable national legal framework/ Reference** Section 5 2003:615 **Additional Information** General timeline for ethical review: in practice, it usually takes approximately 30 days for both EC and CA.
Amendments/ Substantial Amendments (SA)	**Ethical review mandatory for** Any substantial amendments **Responsible for notification of SA** Sponsor

Timeline Ethical review of SA (max nr days)

35
From date of receipt of valid application

Guidance on submission of SA

A guide to the application (including the submission of amendments) is provided on the EPN website in section Application.

Applicable national legal framework/ Reference

Chapter 6 (2&3) LVFS 2003:6

Additional Information

Some amendments do only require notification to the CA and a favourable opinion by the EC.

The sponsor ensures that a copy of the EC's opinion is submitted to the MPA within 15 days after receipt.

Safety Reporting

Reportable AEs

SAE (Serious Adverse Event)
SUSAR (Suspected Unexpected Serious Adverse Reaction)

Investigator shall report SAE to

Sponsor

Reporting timeline

Immediately (without delay)

Responsible for AE reporting to relevant EC(s)

Sponsor

SUSAR being life-thereatening or leading to death must be reported

Within a max of 7d upon first knowledge (+ 8d for additional information)

All other SUSAR must be reported

Within a max of 15d upon first knowledge

SAE/SADE must be reported

–

Sponsor is obliged to notify all investigators of SAE/ SADE occurrence

Yes

National Standard Reporting form available

–

Reporting format - Options

–

Preferred reporting format

–

Provision of Annual safety report mandatory

Yes

Applicable national legal framework/ Reference

Chapter 6 (11-18) LVFS 2003:6

	Additional Information In case of acute danger or risk to the study participants, the sponsor is obliged to inform the CA and the EC without delay of the measure taken (Chapter 6 (4) LVFS 2003:6) NB: In practice, ECs do NOT want undigested SAE or SUSARS. They accept national reports, but prefer a report with a statement if the event affects the risk-benefit evaluation]
End of Trial	**End of trial Declaration mandatory** No **Responsible for End of trial Declaration** – **Regular Termination - Declaration timespan (max nr days)** – **Timespan counted from** – **Early/premature Termination - Declaration timespan (max nr days)** – **Additional Information** No explicit declaration obligations to ECs are legally fixed in the Swedish Acts (GCP is regulated in the Drug Act, but mostly referred to and not incorporated; GCP not a part of the Act regulating the ECs, however it is also here referred to). So in practice, very few reports are submitted to ECs, e.g., in the case of: the sponsor is a company, the declaration and final report are sent to ECs because the company SOPs ask for it. a new application, if this is a continuing work, based on a previously approved study. There is no offense in no shipping reports to ECs, taking for granted that they have been shipped to the CA.
Additional Information & Specifics	**Additional Information** Special requirements are applicable for: (1) Sampling of biological material is regulated by the Swedish Biobank legislation- further information is provided on the Swedish Biobank website. (2) Genetic testing currently requires permission from the Data Inspection Board before submission to the EC. (3) Other interventional biomedical research, for example physiotherapy, only requires submission to the EC. (4) Some observational studies which involve biological sampling may require submission also to the MPA after EC assessment. (5) Quality studies (usual care) can be submitted to the EC for guidance, but this is not obligatory. (6) Submission of authorisation application to the National Board of Health and Welfare NBH/ Socialstyrelsen is not required at the moment, but may be so in the future for some types of human biomedical research. However, the NBH is the authority supervising biomedical research in the health care setting other than clinical trials of medicinal products or medical device.

Study specific Requirements

Sponsor	**Sponsor - Definition available in national law** Yes

	Sponsor - Definition (pursuant to national law) Sponsor (pursuant to Art 3 LVFS 2003:6): an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial; **Sponsorship mandatory** Yes **Sponsorship mandatory - Additional information** For academic studies, the employer of the investigator will formally be the sponsor. (Not the investigator personally). This follows bylaws regulating the work market. **Co-Sponsor - Definition available in national law** No **Co-sponsorship allowed** No
Investigator	**Entitled to be principal investigator** – **Additional Information** Definition of investigator (pursuant to Art 3 LVFS 2003:6): 'a physician or a person following a profession agreed in the Member State for investigations because of the scientific background and the experience in patient care it requires. The investigator is responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the leader responsible for the team and may be called the principal investigator;'
Study Participants - Informed Consent (IC)	**IC is regulated by law** Yes **Informed Consent - Definition/ Requirements** The research may only be carried out if the trial subject has consented to the research after she/ he has previously been given information on the overall plan and purpose of the research, the used methods, the consequences and risks, the identity of the sponsor and the participant’s right to revoke the consent at any time. The consent is to be voluntary, explicit and specific to particular research and is to be documented even if it not given in writing (pursuant to Section 16,17,19 LVFS 2003:460). (The literal definition of Informed Consent is provided in Chapter 1 (3j) LVFS 2003:6, corresponding to the EU Directive 2001/20/EC.) **Applicable national legal framework/ Reference** Section 16,17,19 LVFS 2003:460 Chapter 1 (3j) LVFS 2003:6 **Additional Information** Special provisions apply to vulnerable persons such as minors (less than 18 years of age) or persons incapable of giving consent (in case of illness, mental disorder, weakened state of health) (pursuant to Chapter 3 (2,3) LVFS 2003:6 and Section 18 resp. 20-22 2003:460).
Study Participants - Vulnerable Population	**Minors / Children - Studies allowed** Yes Special provisions apply **Legal framework/Reference (Minors/Children)** Chapter 3 (2) LVFS 2003:6 Section 18 LVSF 2003:460

Incapacitated persons - Studies allowed

Yes
Special provisions apply

Legal framework / Reference (Incapacitated persons)

Chapter 3 (2-3) LVFS 2003:6
Section 20-22 LVFS 2003:460

Emergency situations - Studies allowed

Yes
Special provisions apply

Emergency situation without prior consent of patient or proxy - Studies allowed

No

Conditions allowing trial participation in emergency setting without prior consent

No studies are allowed involving unconscious patients, not even with proxy approval (valid for IMP studies only).
The reason is that it is not forbidden in the ethics act, but in the drug act. (A proxy consent would need a court decision which takes app. 2 weeks).

Legal framework / Reference (Emergency Situation)

Chapter 3 (2-3) LVFS 2003:6
Section 20-22 LVFS 2003:460

Pregnant or breastfeeding women - Studies allowed

No national legal framework available

Specific provisions

No explicit provisions for the conduct of clinical trials on pregnant or lactating women are mentioned in Swedish legislation

National legal framework for protection of vulnerable populations in place

Yes

Applicable legal framework / Reference (Vulnerable Population)

Chapter 3 (2,3) LVFS 2003:6
Section 18 resp. 20-22 LVFS 2003:460

Data Protection

Specific notification timelines before operations start

–

Language of notification

–

Notification format

–

Data Protection Authority/ Agency - Contact Details

Data Inspection Board/ Datainspektionen

Phone

+46 8-657 61 00

Fax

+46 8-652 86 52

E-Mail

datainspektionen@datainspektionen.se

Web address

http://www.datainspektionen.se/in-english/

Address

Box 8114

ZIP/City

104 20 Stockholm

Country

Sweden (SE)

Additional Information

According to the applicable law (Data Protection Acts and Ordinances), the processing and treatment of integrity-sensitive personal data (e.g. genetic predisposition that appear in a genetic study) shall be notified to the Swedish Data Inspection Board for control (in advance).

Further information is provided on the website.

Legal framework (on safeguarding the collection, handling, recording, keeping and/or processing of any clinical trial related data and patient files)

–

Insurance

Liability insurance or alternative arrangements for damages mandatory for

Study participants

Responsible for covering insurance

Sponsor

Applicable national legal framework/ Reference

Patient Injury Act SFS 1996:799 (Chapter 3 (13) LVFS 2003:6)

Additional Information

The study participants are covered by the above mentioned Patient Insurance LÖF via each County Council and/or the medicinal product insurance ("Pharmaceutical Insurance").

The Pharmaceutical insurance is voluntary and owned by membership to the Swedish Pharmaceutical Insurance Association (Läkemedelsförsäkringen). The insurance covers almost all clinical trials performed by the vast majority of companies operating in Sweden. Sponsors who are employed by universities need to ensure that they are covered by insurance. The professionals involved in clinical trials are covered by the public professional insurance.

National legislation

General Information: Applicable Legislation & Conventions

Official website providing relevant national legislation available

Yes

Official website providing relevant national legislation

Medical Products Agency:
Applicable national acts and codes of statutes (LVFS) issued by The Medical Products Agency are available on the website in section: Legislation

	Official governmental legal database available Yes **Official governmental legal database** Further Swedish legislation can be found on the Sveriges Riksdag website. **Additional Information** All current laws are published in the Swedish Code of Statutes (in Swedish only). Copies of the Code are kept at the Library of the Riksdag and most public libraries. Full-text electronic versions of valid laws and ordinances are available in Swedish on the Riksdag website.
Clinical Trials on IMPs in Humans	**Applicable national regulations** National Act on Medicinal Products Other **Transposition of (CT) Directive 2001/20/EC (or comparable national legal framework)** (1) Medicinal Products Act SFS 1992:859 (in Swedish) (2) LVFS 2003:6 (en/sv): The Medical Product Agency's provisions and guidelines on clinical trials of medicinal products for human use These regulations also apply to radioactive medicinal products, products manufactured using gene technology as well as natural remedies, homeopathic products and certain external remedies. **Transposition of (GCP) Directive 2005/28/EC** – **Other applicable regulations/ implementing provisions (Acts, laws, decrees, ordinances, circulars, etc)** Insurance: Patient Injury Act (Patientskadelag, SFS 1996:799)
Radiation & Radiotherapy	**Use of radiation or radioactive compounds - Specific requirements** Yes **Applicable legal framework** Swedish Radiation Protection Act SFS 1988:220. Unofficial English translation is provided on the Swedish Radiation Safety Authority website. **Additional Information** NB! If ionising radiation or radiological methods are used: Additional approval from Local Radiation Protection Committees (at university hospitals) is required!
Gene Therapy	**Specific requirements** Yes

	Applicable legal framework For clinical gene therapy: • LVFS 2003:6 - The Medical Product Agency's provisions and guidelines on clinical trials of medicinal products for human use (see the unofficial English translation: LVFS 2003:6 English version) Due to the fact that gene therapy medicinal products are covered by LVFS 2003:6 the legal procedure is generally the same as for medicinal products for human use (see chapter 1 guideline to 1 § of LVFS 2003:6). Exceptions and peculiarities for gene therapy are provided in Chapter 5 5 § and 6 § of LVFS 2003:6 (EC review) and Chapter 3 guideline to 3 § of LVFS 2003:6 (Data protection). If GMO are involved, the following regulations/ ordinances have to be additionally considered: • SFS 2000:271 Genetically Modified Organisms (Contained Use) Ordinance • SFS 2002:1086 Genetically Modified Organisms (Deliberate Release) Ordinance • LVFS 2004:10: Medical Product Agency's Regulation on Deliberate Release of Medical Products Containing or Consisting of Genetically Modified Organisms • SWEA Provisions/ Statute Book: AFS 2011:2 Contained Use of Genetically modified Micro-organisms (available in English). As a matter of principle Good Manufacturing Practice (GMP) is required for the manufacture of medicinal products for human use. The EC-GMP-Guideline covers this issue.
Biobanking	**Specific requirements** Yes **Applicable legal framework** Biobanks in Medical Care: SFS 2002:297 **Additional Information** Sampling of biological material is regulated by the Swedish Biobank legislation- further information is provided on the Swedish Biobank website.
Data Protection	**Legal framework (on safeguarding the collection, handling, recording, keeping and/or processing of any clinical trial related data and patient files)** National Data Protection Act Implementing Decrees and Ordinances Other legislation covering DP related issues **National DP act** (1) Personal Data Act: SFS 1998:204 (2) Patient Data Act (Patientdatalag, SFS 2008:355). The Act provides coherent regulation of the processing of personal data in the healthcare sector (how medical records must be kept for all patient care and how the information may be used by the health care providers' staff). The purpose of the legislation is to ensure increased patient security and protection of patients' privacy. **Implementing decrees / ordinances** Personal Data Ordinance: SFS 1998:1191 **Additional Information** Handling of personal data must comply with the applicable Swedish Data Protection Acts and Ordinances (pursuant to Chapter 3 (3) LVFS 2003:6). The unofficial English versions of the above mentioned Acts and Ordinances are provided on the Datainspektionen website in section Legislation.

EC operations/ Fees	**Separate legal framework available** Yes **Applicable legal framework** Relevant provisions and regulations are specified in: • Ethical Review Act: SFS 2003:460 (concerning Ethical Review of Research involving Humans) • Statute SFS 2003:615 (this statute covers regulations in connection with the Ethical Review Act) • Statute SFS 2007:1069 (Instructions for Regional Ethical Review Boards) • Statute SFS 2007:1068 (for the Central Ethical Review Board) **Additional Information** The unofficial English versions of the above mentioned Act and Statutes are provided on the Central EC's website in section Regulations.

Definition

IMP/IMP Study	**IMP - Definition available in national law** Yes **IMP - Definition** IMP (pursuant to Chapter 1 (3) LVFS 2003:6): 'A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.' **IMP Study - Definition available in national law** Yes **IMP Study - Definition** Clinical trial (pursuant to Chapter 1 (3) LVFS 2003:6) 'any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy; This includes clinical trials carried out in either one site or multiple sites, whether in one or more than one Member State.