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Pharmacovigilance and Epidemiology Department

Technical specifications for open invitation to tender

Procurement procedure no. EMA/2017/09/PE – Efficacy and safety studies on medicines

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30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Technical specifications for open invitation to tender

No. EMA/2017/09/PE – Efficacy and safety studies on medicines

1. Title of the invitation to tender

This document contains the technical specifications for the open invitation to tender no. EMA/2017/09/PE for efficacy and safety studies on medicines.

Executive summary & indicative timetable

Item	Summary
Contracting authority	European Medicines Agency hereinafter referred to as "EMA" or "the Agency"
Purpose	Performance of post-authorisation efficacy and safety research to generate evidence to support regulatory decision-making. The specific studies may concern the research described under Lots 1 to 4 below • Lot 1: Use of innovative methods to optimise the utility of sparse data to support benefit/risk assessment • Lot 2: Qualitative research • Lot 3: Pharmacoepidemiology research – rapid descriptive studies • Lot 4: Pharmacoepidemiology research - association studies, including pregnancy and breastfeeding research
Contracts	Maximum of five framework contracts per lot for Lots 1, 2 and 3, and maximum of eight framework contracts for Lot 4 to provide efficacy and safety studies on medicines, as and when required. Framework contracts do not constitute orders. Orders are placed through specific contracts. The framework contract will define the types of services and their corresponding price. Based on these costs, specific contracts may be concluded according to the terms and conditions of the framework contract and of the corresponding financial and technical tender of the contractor.
Duration of framework contracts	Four years.
Place of delivery	Services are to be performed at the contractor's premises. Results of services are to be delivered to the Agency.
Volume (indicative)	Up to four studies per lot per year; the budget per study may be up to a

Item	Summary
	maximum of EUR 500,000 each. The indicative maximum budget foreseen for all four lots over four years is EUR 5,000,000. Estimated value per lot: Lot 1: € 400,000 Lot 2: € 600,000 Lot 3: € 1,000,000 Lot 4: € 3,000,000
Joint Offers	Permitted.
Variants	Not permitted.
Subcontracting	Information on all subcontractors must be included in the tenderer's response; additional subcontracting may be proposed at reopening of competition stage for each individual study.
Launch of tender in OJEU	14/12/2017
Deadline for request of clarifications from EMA	26/01/2018 The attention of tenderers is drawn to the fact that the Agency will remain closed from 22 December 2017 until 2 January 2018 inclusive. Any questions submitted during this period will be answered as soon as possible after the Agency has re-opened on 3 January 2018.
Closing date for receipt of tenders	**02/02/2018**
Opening of tenders	08/02/2018
Completion of evaluation of tenders	Q1 2018 (estimated)
Signature of framework contracts	Q2 2018 (estimated)

2. Purpose and context of the invitation to tender

The European Medicines Agency ("the Agency" or "EMA") is a decentralised agency of the European Union (EU) currently based in Canary Wharf in the Docklands area of London (E14). It began operating in 1995. Please note that following the notification to the EU by the UK of its intention to leave the EU under Article 50 of the Treaty on European Union, it has been decided by the European Council that the Agency shall be relocated to Amsterdam. It is envisaged that the Agency will have relocated before the end of March 2019.

EMA's mission is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use.

EMA:

- Supports medicines development by giving scientific advice and providing guidance to developers of medicines;
- carries out robust scientific evaluations of medicines for human and veterinary use that are the basis of the European Commission's decision on whether a medicine can be authorised for marketing throughout the EU;
- monitors the safety of medicines in the EU throughout their lifespan; and
- provides information on medicines to healthcare professionals and patients.

EMA is responsible for the centralised procedure for the authorisation of medicines resulting in a single evaluation and a single authorisation for the whole of the EU. The centralised procedure is compulsory for certain medicines, including human medicines intended for the treatment of HIV/AIDS, cancer, diabetes or neurodegenerative diseases, designated orphan medicines intended for the treatment of rare diseases, and medicines derived from genes, cells, tissue-engineering and biotechnology processes.

EMA coordinates the work of around 4,500 experts made available by the EU Member States. These experts evaluate the medicines and are members of the Agency's scientific committees, its working parties and groups.

The Agency's recommendations on medicines are based on rigorous scientific standards and the available evidence. Pharmaceutical companies applying for a marketing authorisation for a medicine have to submit comprehensive data on the safety, efficacy and quality of their medicine. These data are scrutinised by the Agency's experts, who will recommend the marketing authorisation of a medicine if the data convincingly show that its benefits outweigh its risks.

EMA is a scientific body. Decisions on whether to grant, suspend or revoke a marketing authorisation for centrally authorised medicines are issued by the European Commission, based on the Agency's scientific opinions. Once granted by the European Commission, the centralised marketing authorisation is valid in all EU and EEA-EFTA states (Iceland, Liechtenstein and Norway). This allows the marketing authorisation holder to market the medicine and make it available to patients and healthcare professionals throughout the EEA.

The Agency is responsible for coordinating the EU's pharmacovigilance system for medicines. It constantly monitors the benefit-risk balance of medicines through the EU network and can take action if information indicates that the balance of a medicine has changed since it was authorised. The Agency also monitors the subsequent effectiveness of actions taken and the impact of relevant legislation.

3. Subject of the tender

3.1. Context

The benefit/risk balance of a medicinal product at the time of its initial marketing authorisation is based on evidence generated by a clinical development programme. Appropriate risk management systems are adopted to ensure the safe and effective use of the medicine post-authorisation. Building knowledge throughout the lifetime of a medicinal product is therefore critical in fully characterising the safety and effectiveness profile of a medicine and thus its benefit/risk balance while it is marketed.

While valid scientific evidence generated by an MAH remains at the core of regulatory evaluation, additional and relevant data and information available from alternative sources or new data may be generated to inform regulatory decision-making. Technological and scientific developments of recent years provide unprecedented opportunities to further support regulatory decisions based on the best available scientific evidence.

The EMA needs to have access to scientific expertise in selecting and using methods appropriate to a wide range of safety issues and in understanding the evidence needed for regulatory decision making.

Many of the questions raised by the EMA and its advisory committees can be addressed through analyses of observational health data. Thus the EMA needs also to collaborate with research organisations with established expertise in analysis of such data. Because the objective of these studies is often to resolve a current and ongoing safety concern the time frame may be short and hence immediate access to retrospective electronic health records is an advantage. Since data concerning specific problems may be sparse, access to more than one dataset using state-of-the-art methods to achieve rapid and equivalent analyses in different datasets will, on occasions, be necessary.

3.2. Technical specifications

The Agency considers that it may require the services of research organisations to perform post-authorisation effectiveness and pharmacoepidemiology studies to generate data and information to support regulatory decision-making. Research studies may also focus on the effectiveness of regulatory measures taken and on the impact of relevant legislation. Research topics are those with high public health relevance and with a European impact. The scope of the funding covers both nationally and centrally authorised products, including vaccines. The results obtained from this research will subsequently be assessed by the responsible Agency Committee regarding the need for regulatory action and further research may subsequently also be conducted to measure the effectiveness of regulatory actions taken. To conduct this research the Agency as a first step seeks to put in place framework contracts with a maximum of five research organisations per lot for lots 1, 2 and 3, and a maximum of eight research organisations for lot 4, for a period of four years each. The research organisations with framework contracts will subsequently be invited to submit tenders for specific studies on topics that will be identified by the Agency in collaboration with its Scientific Committees as part of the scientific evaluation of the benefit/risk ratio of authorised medicinal products.

The specific studies may concern the research described under Lots 1 to 4 below.

The Agency seeks to put in place multiple framework contracts for a period of four years each. It is anticipated that a maximum of five framework contracts would be awarded for lots 1, 2 and 3, and a maximum of eight framework contracts would be awarded for Lot 4.

The tenderers may apply for one or several of these Lots.

Lot 1: Use of innovative methods to optimise the utility of sparse data to support benefit/risk assessment

There may be a need to maximise efficiency in the use of available data to support regulatory decision making in relation to a specific concern and to avoid unnecessary further clinical studies. Sparse data may contribute to estimation of risks and identification of sub-groups of the population most at risk in order to optimise the use of medicines. To this end there is an increasing interest in the use of innovative methods to optimise the use of sparse data such as pharmacokinetic or pharmacodynamic markers of the biological activity of a particular class of medicines and the associated risk of specific adverse outcomes, or data in special populations (children, organ-impaired, the elderly). These

methods may include modelling and simulation and/or extrapolation approaches. Skills required to conduct such work should include:

- Data management to support the application of statistical and computational methods to data that may come from more than one source.
- Use of state-of-the art methods in modelling and simulation techniques to optimise the use of sparse data.
- An understanding of the regulatory reporting and qualification requirements to support the use of modelling and extrapolation in regulatory decision-making.

Lot 2: Qualitative research

Qualitative research provides information about the prescription and use patterns of medicines and associated behaviours, including explorations of motivations, beliefs, feelings and experiences of patients and health professionals. The underpinning of qualitative research requires multiple methodological approaches with different theoretical origins and tools. Skills required to conduct such work include knowledge of qualitative:

- theories: such as action research and case studies (potential for a mixed-methods approach), ethnography (for the study of social interactions, behaviours, and perceptions within groups, organisations and communities), phenomenology (for studying an individuals lived experience of events), and grounded theory (for generating new theories regarding social phenomena).
- data generation: such as the use of focus groups, in-depth interviews and sampling strategies.
- data analysis: using deductive and inductive approaches such as content analysis, discourse analysis, thematic analysis, grounded theory and triangulation of data.

Lot 3: Pharmacoepidemiology research – rapid descriptive studies

Not all safety research involves causal analyses, and quantitative knowledge of descriptive epidemiology and drug utilisation may be required. On some occasions, questions raised by the EMA and its advisory committees, such as extent of drug exposure in a population, distribution of indications for prescribed drugs in clinical practice or numbers of cases of a suspected drug reaction within a defined time window following drug exposure, need to be answered very rapidly, i.e. within a few weeks.

In this context, Lot 3 concerns rapid descriptive analyses performed across multiple European databases.

Under Lot 3 a mechanism should be established by which specified descriptive analyses could be performed across multiple databases within a maximum of two months. This involves having access to at least three European databases and being able to provide responses to specific queries within a short timeframe. Tenderers should have fast access to databases and may propose use of innovative methods or tools such as harmonised coding systems and/or common data models. Examples of questions that may need a fast answer include:

- Calculation of prevalence or incidence rate of a disease or condition
- Description of products prescribed or used for a particular indication or condition or in particular demographic groups, and treatment patterns
- Estimates of exposure to a medicinal product (or concomitant exposures to two or more medicinal products) and crude incidence of defined health outcome of interest within a defined exposure time

- Preliminary estimates of the impact of pharmacovigilance measures in simple terms, for example changes in usage of both affected medicinal product and other alternative products

The number of databases and their geographical spread that can be accessed by the tenderer (i.e. either via existing in-house access or via agreements in place with data owners) will be an element of appreciation and taken into consideration in the scoring under the qualitative award criteria (see section 14.1.).

Lot 4: Pharmacoepidemiology research – association studies, including pregnancy and breastfeeding research

This lot may concern a wide range of research questions, including those listed for Lot 3 as well as more complex studies where the association between an exposure and a health outcome needs to be determined taking into account potential confounding factors, including time-varying factors, effect modifiers and sources of biases. The tenderer should be able to perform a broad range of descriptive or more complex association studies in databases in at least two European countries and use different approaches relevant for the research question, including systematic reviews and meta-analyses. On occasions the questions addressed via a specific study might aim to inform the design or to supplement the results of randomised controlled trials of efficacy. Thus understanding of such trials could also be useful.

This lot may also concern studies conducted to obtain a better understanding of patterns of, and hazards associated with, medicine use in pregnancy and / or breastfeeding.

To help provide such understanding or insights, a range of specific expertise and data sources could be useful. This includes expertise and data to carry out observational studies (drug utilisation and / or risk assessment of medicines used in pregnancy and breastfeeding, using data sources such as disease registries or electronic health records with reliable pregnancy and pregnancy outcome data – including delayed or long term pregnancy outcomes) but also access to other methods and expertise with understanding of assays to reliably detect medicines in breast milk, models for determining placental transfer of medicines, or communication tools to help obtain most reliably complete pregnancy prevention for teratogenic products. The successful tenderer is not expected to have all the expertise 'in house' or in one location necessarily, but it is expected to have access to and establish working relationships with a network of scientists where one or more elements of the expertise described is available where needed.

The number of databases and their geographical spread that can be accessed by the tenderer (i.e. either via existing in-house access or via agreements in place with data owners) will be an element of appreciation and taken into consideration in the scoring under the qualitative award criteria (see section 14.1.).

3.3. Support from the European Medicines Agency

For specific studies, the Agency will provide the successful contractor(s) with access to the information required to perform the studies, including, where applicable, an updated assessment on the medicinal product issue that is the subject of the research.

The Agency supports the conduct of this research in line with the principles and tools for scientific independence, transparency and sound methods of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and recommends registration of studies in the EU PAS Register[1].

[1] http://www.encepp.eu/encepp_studies/indexRegister.shtml

3.4. Minimum requirements to be met by the tender

The following minimum requirements must be met by the tender for it to be considered compliant with the technical specifications. Tenderers must provide a completed declaration which can be found in **Annex IV**. Failure to confirm compliance with all the following requirements shall result in elimination from the tender:

Minimum requirements applicable to all lots

- Compliance with applicable environmental, social and labour law obligations established by Union law, national legislation, collective agreements or the international environmental, social and labour conventions listed in Annex X to Directive 2014/24/EU.
- Ability to communicate with the Agency in English for the seamless implementation and execution of all the services covered within the scope of the contract, including responsibilities resulting from regulatory requirements such as Health and Safety and Data Protection, as well as for the efficient and timely response in respect to contract management.

Minimum requirements applicable to Lot 3 in addition to above

- Access to prescribing, demographic, individual patient risk factor and clinical outcomes data in at least three European countries.

Minimum requirements applicable to Lot 4 in addition to above

- Access to prescribing, demographic, individual patient risk factor and clinical outcomes data in at least two European countries.

4. Participation in the tender

4.1. Agreements on public procurement

Participation in procurement procedures is open on equal terms to all natural and legal persons falling within the scope of the Treaties. This includes all legal entities registered in the EU and all natural persons having their domicile in the EU. Participation is also open to all natural and legal persons registered or having their domicile in a non-EU country which has an agreement with the European Union in the field of public procurement on the conditions laid down in that agreement. The rules of access to the market do not apply to subcontractors.

The procurement procedures of the Agency are not however open to tenderers from countries which have ratified the Multilateral Agreement on Government Procurement ("GPA").

4.2. Subcontracting

If the tender envisages subcontracting any part of this contract, **Annex V** should be completed indicating clearly the identity, roles, activities and responsibilities of subcontractor(s) and specifying the volume/proportion for each subcontractor.

Attached to the completed **Annex V** should be a signed letter of intent by each subcontractor stating its unambiguous undertaking to collaborate with the tenderer if it wins the contract and the extent of the resources that it will put at the tenderer's disposal for the performance of the contract. This also applies to any additional subcontractors that are being proposed at reopening of competition stage.

A completed **Annex III** is required by all identified subcontractors. Tenderers should note their obligation to replace a subcontractor if it is in an exclusion situation or does not meet a specific selection criterion.

If such documents are not provided, the Agency shall assume that the tenderer does not intend to subcontract.

Supplementary information on subcontracting:

- The same legal entity may participate simultaneously as a group member for one lot, and as a subcontractor for another lot.
- Subcontracting of one and the same legal entity in more than one lot is acceptable.
- There is no limit to the volume/proportion of the tender being subcontracted.

4.3. Joint offers

Joint offers are permitted – for further information on types of collaboration see also section 5. of the Agency's *Guidebook for Tenderers*[2].

In case of a joint offer, an overview should be provided indicating clearly the identity, roles, activities and responsibilities of each individual partner.

Supplementary information on joint offers:

- The principle of 'one tender per tenderer' applies. It therefore follows that the same legal entity may not participate as a group member in more than one tender for the same lot (e.g. two different departments from the same academic institution would be considered the same legal entity).
- The group members are required to nominate a lead representative who is empowered to submit the tender on behalf of all partners and to act as the main contact point for the Agency (see also: cover letter in Annex 1a).

4.4. Identification of the tenderers

The tender must include a cover letter drafted using the appropriate template provided in Annexes Ia and Ib to this document. The cover letter must present the name of the tenderer (including group leader and all members of the tendering group in case of a joint tender) and identified subcontractors if applicable, and the contact information of the single contact person in relation to this tender.

In case of a sole tenderer, the cover letter must be signed by the person(s) empowered to represent the tenderer and entitled to sign the contract in case the offer is successful.

In case of a joint tender, the cover letter must be signed by (a) duly authorised representative(s) for each member of the tendering group.

5. Additional documentation available to tenderers

Further information about the work of the Agency can be obtained on its website: http://www.ema.europa.eu.

[2] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/03/WC500203892.pdf

Further information about the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) can be obtained on its website: http://www.encepp.eu

6. Site visit – not applicable

7. Variants – not applicable

8. Estimated contract volume

Without this being binding, the Agency estimates that up to four specific efficacy and safety research studies may be required per lot per year. Typically, the budget per study may be approximately €60,000 to €500,000.

The maximum budget foreseen for all four lots over four years, without this being binding, is €5,000,000.

The framework contract value per lot over the contract duration of four years is estimated as follows:

Lot no.	Description	Contract value (in EURO)
1	Use of innovative methods to optimise the utility of sparse data to support benefit/risk assessment	€400,000
2	Qualitative research	€600,000
3	Pharmacoepidemiology research – rapid descriptive studies	€1,000,000
4	Pharmacoepidemiology research - association studies, including pregnancy and breastfeeding research	€3,000,000

The Agency may exercise the option to increase the financial ceiling per lot at a later stage via negotiated procedure for the repetition of similar services in accordance with Article 134 (1) (e) of the Rules of Application of the general Financial Regulation[3]. This procedure may only take place at the latest during the three years following contract signature, and shall be triggered by the need to increase the financial ceiling up to a maximum of 50% of the initial ceiling.

9. Price

9.1. Currency of tender

Prices should be submitted in Euro. The appropriate costing sheet per lot attached to these specifications must be used to submit a financial tender – **Annex II.1-4**.

Please note that the financial costing sheet(s) in **Annex II.1-4** must be submitted in separate binders or folders and in a separate envelope from the rest of the tender submission. The costing sheet(s) must also be provided on separate CD-ROM/DVD/USB memory stick which must be clearly labelled.

[3] Part 1, Title V of Commission Delegated Regulation (EU) No 1268/2012 of 29 October 2012 on the rules of application of Regulation (EU, Euratom) No 966/2012 of the European Parliament and of the Council on the financial rules applicable to the general budget of the Union, as amended.

9.2. All-inclusive prices

Prices submitted in response to this tender must be inclusive of all costs involved in the performance of the contract (e.g. to include travel, subsistence etc.). No expenses incurred in the performance of the services will be reimbursed separately by the Agency.

9.3. Price revision – not applicable

9.4. Costs involved in preparing and submitting a tender

The Agency will not reimburse any costs incurred in the preparation and submission of a tender. Any such costs must be paid by the tenderer.

9.5. Period of validity of the tender

Tenderers must enclose a confirmation that the tender (including prices) is valid for nine months from the closing date for receipt of tenders.

9.6. Protocol on the Privileges and Immunities of the European Union

The Agency is, as a rule, exempt from all taxes and duties, and in certain circumstances is entitled to a refund for indirect tax incurred such as value added tax (VAT), pursuant to the provisions of Articles 3 and 4 of the Protocol on the Privileges and Immunities of the European Union. Tenderers must therefore give prices which are exclusive of any taxes and duties and must indicate the amount of VAT separately.

10. Payment arrangements

The successful contractor, to which a specific contract is awarded following a re-opening of competition, will be requested to establish a list of all pre-existing rights and rights of creators and third parties on the results of this specific contract or parts thereof. This list must be provided no later than the date of delivery of the final study results. The Agency will provide a form for this purpose which must be attached to any interim or final invoice.

In accordance with the contract, payments shall be made in arrears following receipt of an invoice and completion of services. A detailed payment schedule will be provided for each individual specific contract. Payments are linked to the formal acceptance of individual deliverables by the Agency, and will be effected upon reaching certain milestones (e.g. acceptance of study protocol, acceptance of study report).

Payments shall be made within 60 days of receipt of the request for payment and shall be deemed to have been made on the date on which they are debited to the Agency's account. The Agency may, however, after giving notice to the tenderer, defer payment if the products or services covered by the request for payment are contested by the Agency.

All invoices shall be sent in PDF format to the following e-mail address: ema.vendorinvoices@ema.europa.eu.

The Agency shall be bound to comply with payment periods only if requests for payment are properly presented at the above address.

The tenderer is required to give the following information on all invoices:

- The breakdown of fees for services, the contract price and the amount of VAT applied, if any, or, whenever appropriate, a note that the services rendered under the contract are exempted from VAT in accordance with the national tax law by which the tenderer is governed.
- A reference to the specific contract number.
- A reference to the Agency's purchase order number which shall be communicated from time to time.

11. Contractual details

A draft contract is attached to these Technical Specifications as **Annex VI.** Tenderers must confirm acceptance of the draft contract and terms and conditions of the tender as part of their tender response in the appropriate cover letter provided in **Annex Ia or Ib**.

Tenderers' attention is drawn to the fact that the *ENCePP Code of Conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies*[4] will be an integral part of, and shall prevail over, the framework contract. Notwithstanding any other term of the framework contract, or any resulting specific contract, and in line with the provisions of the Code, the contractor will be granted license to make use in future research and for teaching purposes of any study results generated for the Agency under the contractual arrangement. Furthermore, the contractor shall have the freedom to publish without restriction any research results generated for the Agency under any specific contract.

The Agency wishes to conclude a maximum of five framework contracts for lots 1, 2 and 3, and a maximum of eight framework contracts for lot 4 to provide efficacy and safety research, as and when required, for a period of four years each. A framework contract will establish the terms governing specific contracts to be awarded during a given period, in particular with regard to price. Specific contracts shall be awarded on the basis of reopening of competition for each study.

Whilst the Agency wishes to conclude up to five framework contracts per lot (lots 1, 2, 3), respectively up to eight framework contracts per lot (lot 4), the very minimum number of framework contracts will usually be three per lot. This is to ensure genuine competition during the lifetime of the framework contracts. If there is only one acceptable tender per lot, the procedure for this particular lot will be cancelled.

Signature of the framework contract imposes no obligation on the Agency to order services. Only the implementation of the framework contract through specific contracts is binding for the Agency.

Each specific contract will contain details of deliverables and timelines for particular services to be provided.

The award criteria for reopening of competition (specific contracts under the framework contract) are provided for information in Annex VIII.

11.1. Implementation of the framework contract

1. Whenever the Agency decides that a research study in support of regulatory decision making is required, it will reopen the competition among all the framework contractors within a specific lot.
2. The Agency will draw up the technical specifications, including background information, details of deliverables and timelines.

[4] http://www.encepp.eu/code_of_conduct/index.shtml

3. The Agency will send these specifications to all framework contractors for the specific lot and specify a deadline (minimum 2 weeks) by which the technical and price offers need to be submitted to the Agency in the form of a detailed research proposal.
4. Within 5 working days of receipt of the specifications, the contractors shall send by email an acknowledgement of receipt and express their intention to carry out the services required. The contractors should provide justification in case they do not intend to submit an offer.
5. The contractors submit their technical and price offer, including proposal of subcontractor(s) within a minimum of two weeks, or other deadline which may be communicated by the Agency.
6. The Agency will assess the offers by an evaluation committee consisting of EMA staff, and award the contract to the most economically advantageous tender, based on the award criteria provided in Annex VIII of this document. The Agency also takes into account any conflicting interests which may negatively affect the performance of the specific contract.
7. The Agency will notify its decision to the contractor and may sign a specific contract with the contractor which has submitted the most advantageous offer. The specific contract shall confirm the charges payable for the research study performed.
8. Within 15 working days of a specific contract being sent by the Agency to the contractor, the Agency shall receive it back, duly signed and dated.

11.2. Research teams in the specific contract

A table with the composition of the team and the role of each member shall be provided by the contractor for each specific request.

A declaration of professional conflicting interests shall be provided for each member of the proposed research team.

Any change of expert involved in the specific contract shall be notified to and agreed with the Agency, subject to assessment of professional conflicting interests in relation to the topic of the research request.

11.3. Deliverables of specific contracts

Typically, the contractor may be requested to provide the following deliverables, although this list may vary depending on the individual research question:

- **Preliminary study plan**
- **Study protocol** – the protocols should follow the format described in GVP Module VIII[5], section VIII.B.3.1.)
- **Study report** - the reports should follow the format described in GVP Module VIII[3], section VIII.B.4.3.2.)
- **Manuscript** – the manuscript should be suitable for submission to a peer-reviewed medical journal and include the following standard disclaimer: "*This document expresses the opinion of the authors of the paper, and may not be understood or quoted as being made on behalf or of reflecting the position of the European Medicines Agency or one of its committees or working parties.*"

  The published article shall be available with open access.

[5] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf

The Agency expects that specific studies are conducted in line with the ENCePP principles and tools for scientific independence and transparency, and as such are registered in the European Union electronic Register of Post-Authorisation Studies (EU PAS Register[6]). The *ENCePP Code of Conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies*[7] will be an integral part of the framework contract.

11.4. Results and intellectual property rights

The provisions on the use of the research results and ownership of the research results can be found in the draft framework contract (Article I.10 Exploitation of the results of the contract and Article II.13 Intellectual Property Rights). Tenderers are advised to familiarise themselves with these contractual provisions.

Tenderers' attention is drawn to the fact that the *ENCePP Code of Conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies* will be an integral part of, and shall prevail over the framework contract. Notwithstanding any other term of the framework contract, or any resulting specific contract, and in line with the provisions of the Code, the Contractor is granted a non-exclusive, irrevocable, royalty-free license to make use in future research and for teaching purposes of any study results generated for the Agency under the Contract. Furthermore, the Contractor shall have the freedom to publish without restriction any research results generated for the Agency under the Contract.

The research results must be forwarded to EMA. The copyright of the study results will belong to the Agency; the Agency will in particular have the right to publish the results, including the structured final data.

At the time of submitting a tender to a re-opening of competition the tenderer must provide information about the scope of pre-existing materials, their source and when and how the rights to these materials have been or will be acquired. In the tender proposal all quotations or information originating from other sources and to which third parties may claim rights have to be clearly marked (source publication including date and place, creator, number, full title etc.) in a way allowing easy identification.

The successful contractor, to which a specific contract is awarded following a re-opening of competition, will be requested to establish a list of all pre-existing rights and rights of creators and third parties on the results of this specific contract or parts thereof. This list must be provided no later than the date of delivery of the final deliverable that is subject of the specific contract. The Agency will provide a form for this purpose which must be attached to the final invoice.

12. Exclusion criteria

All tenderers and identified subcontractors shall provide a declaration on their honour (see **Annex III**), duly signed and dated by an authorised representative, stating that they are not in one of the situations of exclusion listed in this Annex.

The successful tenderer shall provide the documents mentioned as supporting evidence in **Annex III** before signature of the contract and within a deadline given by the Agency. The Agency may request that supporting evidence be provided by subcontractors.

[6] http://www.encepp.eu/encepp_studies/indexRegister.shtml
[7] http://www.encepp.eu/code_of_conduct/index.shtml

The Agency may waive the obligation of a tenderer to submit the documentary evidence referred to above if such evidence has already been submitted to it for the purposes of another procurement procedure and provided that the issuing date of the documents does not exceed one year and that they are still valid. In such a case the tenderer shall declare on its honour that the documentary evidence has already been provided in a previous procurement procedure and confirm that no changes in its situation have occurred.

Tenderers should note that there will be an obligation to replace a subcontractor if it is in an exclusion situation.

New subcontractors added at reopening of competition stage may be requested to complete Annex III and to provide supporting evidence.

13. Selection criteria

13.1. Legal and regulatory capacity

13.1.1. Requirement:

All tenderers must have authorisation to perform the contract under national law.

13.1.2. Evidence required:

The following shall be provided only once, regardless of the number of chosen lots.

All tenderers (and each partner in the case of joint offers) and identified subcontractors shall provide a declaration on their honour (see **Annex III**), duly signed and dated by an authorised representative, as part of their tender response, stating that they have the legal and regulatory capacity to pursue the professional activity needed for performing the contract to meet the requirement as stated in ***13.1.1.***

The tenderer (and each partner in case of joint offers) shall provide the following evidence listed below upon request by the Agency at any time during the procurement procedure:

- Authorisation to perform the contract under national law, as evidenced by inclusion in a relevant professional or trade register (except for international organisations), membership of a specific professional organisation, express authorisation of entry in the VAT register.

The Agency may request that supporting evidence be provided by subcontractors.

13.2. Financial and economic capacity

13.2.1. Requirement:

- Tenderers must be financially feasible and in a stable financial position and have the economic and financial capacity to perform the contract.
- In order to be financially feasible, an entity must be able to demonstrate a favourable total score for the following: liquidity, capability to cover its short-term commitments; solvency, capability to cover its medium and long-term commitments; and profitability, generating profits, or at least with self-financing capacity.

13.2.2. Evidence required:

The following shall be provided only once, regardless of the number of chosen lots.

All tenderers shall provide a declaration on their honour (see **Annex III**), duly signed and dated by an authorised representative, as part of their tender response, stating that they fulfil the applicable financial and economic criteria set out in ***13.2.1***.

If the tenderer is a company and is otherwise required under the law of the State in which it is established to publish its accounts, it shall provide upon request by the Agency at any time during the procurement procedure, including from subcontractors if requested:

1. financial statements or their extracts for the last two financial years for which accounts have been closed;
2. a statement of overall turnover for the last two financial years available.

If, for some exceptional reason which the contracting authority considers justified, the tenderer is unable to provide the documentation mentioned, it may prove its financial and economic capacity by any other means which the contracting authority considers appropriate.

If the tenderer relies on the capacities of other entities (e.g. a parent company), a written undertaking on the part of those entities confirming that they will place the resources necessary for performance of the contract at the disposal of the tenderer for the period of the contract may be requested by the Agency. In such case the Agency may require that the successful tenderer(s) and such entities are jointly liable for the execution of the contract.

The Agency may waive the obligation of a tenderer to submit the documentary evidence referred to above if such evidence has been submitted to it for the purposes of another procurement procedure and provided that the documents are up-to-date.

The following ratios will be calculated to evaluate financial feasibility:

Ratio	Formula	Scoring		
		0	1	2
Liquidity	*Liquidity* Current assets – Stocks – Debtors > 1 year Short term debts	Below 50%	Between or equal 50% and 100%	Above or equal 100%
Solvency	*Financial independence* Own funds Total liabilities	Below 20%	Between or equal 20% and 40%	Above or equal 40%
	Debt ratio Own funds Medium- and long-term debts (MLT)	Below 30%	Between or equal 30% and 60%	Above or equal 60%
Profitability	*Coverage of deposits and borrowed funds by Self Financing Capacity (SFC*)* SFC Medium and long terms debt (MLT) * SFC = net result + amortisation	Below 25%	Between or equal 25% and 50%	Above or equal 50%
	Profitability Gross operating result Turnover	Below 5%	Between or equal 5% and 15%	Above or equal 15%

A score is awarded according to the calculated values of each of the five ratios and the maximum score an entity may obtain is a total of 10 points.

In order to meet the financial capacity criterion, the tenderer must obtain a score of at least 4 points out of 10.

If it seems that the financial feasibility evaluation does not provide a favourable picture of an organisation's financial status, economic and financial capacity may be proven by any other means which the contracting authority considers appropriate.

In case of joint tenders the financial and economic capacity shall be evaluated as a whole.

13.3. Technical and professional capacity

13.3.1. Requirements:

The criteria for this framework contract are:

A. For each lot being tendered for, the tenderer must have experience in conducting research in the domain and have research commissioned by an external source.

B. The tenderer shall have access to a multi-disciplinary research team for each lot tendered. The team shall be led by (a) responsible senior investigator(s) with a strong (PhD level) academic background in one of the life sciences, and at least 5 years' experience in research.

For Lots 3 and 4 only:

C. The tenderer must be able to ensure high quality service through access to or collection of appropriate data relevant to lots 3 and 4 (as detailed in section 3. 'Subject of the tender').

Tenderers for lots 3 and 4 must meet all of the above requirements.

Tenderers for lots 1 and 2 must meet criteria A. and B.

13.3.2. Evidence required:

All tenderers (and each partner in the case of joint offers) shall provide a declaration on their honour (see **Annex III**), duly signed and dated by an authorised representative, as part of their tender response, stating that they fulfil the applicable technical and professional criteria set out in ***'13.3.1 Requirements'.*** This shall be provided once, regardless of the number of chosen lots.

The tenderer shall provide the documents listed below upon request by the Agency at any time during the procurement procedure. For joint tenders the technical and professional capacity shall be evaluated in relation to the tender submitted as a whole, including all group members and subcontractors.

A. For each lot being tendered for, a list of links to relevant publications over the last three years in peer-reviewed journals, or study reports in the public domain, or documentation of relevant unpublished research comparable to the research described in this tender. If more than one lot is being tendered for a combined list may be submitted but it must be grouped by lots.

B. A Curriculum Vitae showing the educational and professional qualifications, skills, experience and expertise of the responsible senior staff member who would lead the research team.

   If more than one lot is being tendered for, a separate CV is required per lot, unless the responsible senior staff member shall be the same for any lot, in which case this should be made clear.

   Curricula Vitae should be submitted without indication of any name. Each should bear a number only and the tender should include a separate list showing the association between these numbers and actual names.

C. Means available for ensuring quality: For Lots 3 and 4 a list of data sets that the tenderer has access to, including a detailed description, size and coverage per data set. Tenderers for Lot 3 should also provide a description of their approach for rapid access to and analysis of descriptive data. If more than one of these lots is being tendered for, a combined list may be submitted but it must be grouped by lots.

13.4. Professional conflicting interest

The verification of professional conflicting interest under the selection criteria refers both to tenderers (including all partners in case of joint tenders) and subcontractors to be engaged in the provision of the service covered by the present procurement procedure. This verification will also apply to any additional subcontractor that is being proposed at the reopening of competition stage.

In accordance with Article 148(6) RAP[8] the EMA may reject tenderers in case of professional conflicting interest that may negatively affect the performance of the framework or any resulting specific contract.

In its assessment EMA will take into consideration if the tenderer and/or subcontractor:

- is a marketing authorisation holder (MAH) or marketing authorisation applicant (MAA) within the territory of the EEA[9];
- is a manufacturer of a medicinal product for which there is a marketing authorisation or ongoing marketing authorisation application within the territory of the EAA;

A declared interest does not necessarily mean to constitute a professional conflicting interest. In its assessment EMA will apply the principle of proportionality laid down in Article 102(1) FR[10].

13.4.1. Evidence required:

The tenderer (including all partners in case of joint tenders) and the identified subcontractor(s) shall sign a declaration of honour stating that it/they is/are not in one of the situations of professional conflicting interest mentioned above (see **Annex III**). This shall be provided once, regardless of the number of chosen lots.

A tender shall be rejected from the procurement procedure if the tenderer has misrepresented the information in this declaration of professional conflicting interests (Article 107(1)(b) FR). Rejection from the procedure on this ground may have serious consequences for the tenderer concerned as it may result in administrative and financial penalties based on grave professional misconduct (Article 106(c)(i) FR).

An assessment of professional conflicting interest based on the above criteria will be carried out by the EMA based on all the documents and information provided in the offer, in particular the evidence for the selection criteria. If necessary (e.g. in case of doubt), the EMA will ask for clarifications regarding the issue.

[8] Commission Delegated Regulation (EU) No 1268/2012 of 29 October 2012 on the rules of application of Regulation (EU, Euratom) No 966/2012 of the European Parliament and of the Council on the financial rules applicable to the general budget of the Union (OJ L 362, 31.12.2012, p. 1), as amended.
[9] Legal or natural persons which control, i.e. own a majority stake in, (i) otherwise exercise a significant influence in the decision-making processes of the relevant MAH/MAA, (ii) are controlled by or (iii) are under common control of a MAH/MAA, shall be considered to be an MAH/MAA.
[10] Regulation (EU, Euratom) No 966/2012 of the European Parliament and of the Council of 25 October 2012 on the financial rules applicable to the general budget of the Union and repealing Council Regulation (EC, Euratom) No 1605/2002 (OJ L 298, 26.10.2012, p. 1), as amended.

The tenderers shall note that if following the assessment the tenderer is found to be in a situation of professional conflicting interest, the corresponding tender will not be further evaluated and will be rejected.

The tenderers and/or the subcontractor are obliged to report to the contracting authority any change in their situation related to the absence of professional conflicting interest throughout the implementation of the contract.

Tenderers shall note that they may be required to provide a detailed 'Declaration of professional conflicting interests' at each re-opening of competition with regard to the specific subject matter of the call.

14. Award criteria

In order to determine the most economically advantageous tender, the award criteria which will apply to this procurement procedure are as follows:

Qualitative award criteria: 70%

Price: 30%

Total 100%

For joint tenders the award criteria shall be evaluated in relation to the tender submitted as a whole, including all group members and subcontractors.

14.1. Qualitative award criteria

Tenderers may apply for one or several of the four lots described in section 3.2. For each lot tendered a separate response per lot is needed for award criterion A. Only one response is required to award criteria B and C, regardless of the number of lots tendered.

The qualitative criteria which will apply equally to all four lots of this tender are set out in tabular format below, including the available points and minimum scores. Any tenderer not achieving the minimum scores indicated below will be eliminated and not evaluated for price. The qualitative award criteria shall account for **70% of the weighting** for this tender.

Generic responses and the mere repetition of mandatory requirements set out in these specifications, without going into details or without giving any added value, will result in a low score.

The sum of all quality award criteria gives a maximum possible of **70 points**.

No.	Qualitative award criterion	Weighting	Maximum points available	Minimum points, which must be achieved
A	Case study	30%	30	18
B	Research Team & Tasks	20%	20	12
C	Project management and communication	20%	20	12
	TOTAL	70%	70	42

A. Case study (30 %)

This criterion will assess the tenderer's overall approach to addressing a request for a study to be conducted taking account of the regulatory context and the tenderer's knowledge of the most recent developments of appropriate methods. The proposal should introduce the scope, define the tasks and set out the preferred methodological approach - or outline a number of different possible approaches.

Tenderers are requested to submit a high-level proposal (max. two pages A4 each) for research in the hypothetical scenario(s) relating to each of their chosen lot(s) as described below. If considered helpful, any relevant supporting documents may be provided in Annex.

Case study – Lot 1: Use of innovative methods to optimise the utility of sparse data to support benefit/risk assessment

A study is required to investigate the extent to which further recommendations can be made in the product information for a class of drugs to improve the interpretation in routine clinical practice of pharmacodynamic markers of their activity. This is to be done using available pharmacokinetic and pharmacodynamic (PK/PD) data linked to clinical outcomes.

The objectives of the study are:

1. To provide comprehensive analyses of the relationship between dose, exposure, PD markers of activity and important efficacy and safety outcomes using currently available data. These analyses are to be conducted for each drug in the class separately and, if scientifically appropriate, using pooled data for more than one drug in the class.
2. To use the results of (1) to determine if the available data allow recommendations to be made regarding a possible role for one or more of these PD markers in clinical practice and/or which data are needed from future research to potentially allow such recommendations to be made.

In terms of methods to be used, a "traditional" dose-exposure-response analysis could be sufficient but a quantitative systems pharmacology approach might be more appropriate to address the research question.

It is, therefore, anticipated that some of the following analyses could be provided:

a) Population pharmacokinetic (PopPK) analysis;

b) Prediction of exposure (Ctrough, Cmax and AUC) at steady state following recommended doses, including exposure predictions in subgroups of particular interest (e.g. elderly, patients with renal impairment, patients on concomitant medication influencing exposure, etc);

c) PK/PD analysis in which:

   - Ctrough, Cmax and AUC would be included as PK exposure variables for drug concentrations;
   - PD variables should include specific markers of biological activity;

d) State-of-the-art modelling and simulation to predict the activity of the drug in virtual patient populations;

e) Methods to support individual risk assessment e.g. sub-group analyses.

Using the exposure measures investigated in the previous analyses, models of individual risk of adverse clinical outcomes should be fitted using drug exposure, PD measures and other factors likely to influence risk (e.g. age, renal function, concomitant medicines). The models used would be scientifically justified and meaningful for clinical practice.

Case study - Lot 2: Qualitative research

To strengthen the safety monitoring of medicinal products, the 2010 EU pharmacovigilance legislation has introduced the concept of additional monitoring for certain medicinal products (see Guideline on good pharmacovigilance practices (GVP) Module X – Additional monitoring (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/04/WC500142282.pdf).

Medicinal products subject to additional monitoring are readily identifiable by an equilateral black triangle that is accompanied by standardised explanatory statements in the product information. It is anticipated that these explanatory statements will encourage patients and healthcare professionals to report suspected ADRs associated with this product.

The proposed study will entail research into the knowledge, attitudes and practices of patients' and healthcare professionals regarding additional monitoring elements, but should not attempt to estimate ADR reporting rates.

This research should evaluate the following aspects:

- awareness of additional monitoring status by patients and healthcare professionals and of medicinal products subject to additional monitoring;
- understanding of the message conveyed by the black symbol and the intended objectives of the additional monitoring status;
- impact of the additional monitoring status on patients' attitude towards reporting of side effects for these products;
- impact of the additional monitoring status on healthcare professionals' attitude towards reporting of suspected ADRs for these products;
- impact of the additional monitoring status on the information healthcare professionals provide to patients to make them aware of the additional monitoring status and its meaning;
- any changes in healthcare professionals' prescribing behaviours induced by the knowledge of the additional monitoring status for a medicinal product.

Case study - Lot 3: Pharmacoepidemiology research – rapid descriptive studies

A medicine for the treatment of poorly controlled asthma has been associated with an increased risk of infections. To guide the design of potential risk minimisation activities, the Pharmacovigilance Risk Assessment Committee require:

- Information on the number of patients exposed to the drug across at least 3 EU member states
- Information on the use in clinical practice of the drug in the stepwise treatment pathway for asthma, e.g. first, second or third line.
- Information on the demographics or comorbidities of the asthma population exposed to the medicine of interest.

A list of databases that can be accessed by the tenderer should be provided.

Case study – Lot 4: Pharmacoepidemiology research – association studies, including pregnancy and breastfeeding research

Potential safety concerns have been identified relating to possible endocrine effects in adolescents following exposure to a specific drug either intra-uterine or while breast-fed. Research is needed to better establish any association and to determine if any sub-groups are at particular risk including in terms of the timing of exposure. The study design should reduce the chance of confounding, and address the challenges of producing comparable results and combining results across data sources.

This research would include efforts to quantify any risk related to exposure and it is also anticipated that efforts would be made to assess causality e.g. use of data from assays to reliably detect medicines in breast milk or models for determining placental transfer of medicine.

A list of databases that can be accessed by the tenderer should be provided.

B. Research team & tasks (20%)

Tenderers are requested to submit a description of the proposed research team roles and distribution of tasks, including the rationale behind the choice of this allocation (max. two pages A4 per lot, preferably in tabular form). This description should relate to a typical research assignment, and not to a particular study.

This criterion will assess how the roles and responsibilities of the proposed team (including subcontractors, if applicable) are distributed for each task, e.g. in protocol development, data extraction and data analysis, interpretation of results, writing of study report and manuscript, etc.

It also assesses the global allocation of resources to the project and to each task or deliverable, and whether this allocation is adequate for the work.

Individuals should not be identified by name, and no Curricula Vitae should be submitted in response to this criterion.

C. Project management & communication (20%)

Tenderers are requested to submit a high-level description of the related project management processes and proposed communication activities, including policy on conflicts of interest (max. two pages A4 per lot). Tenderers are requested to include a description of the mechanisms for assuring a continuous service and quality of deliverables, rapid response and timely availability of the specific expertise required for covering services to be implemented under the Framework Contract. The tenderer's policy on conflicts of interest should also be described. This description should relate to a typical research assignment, and not to a particular study.

This criterion will assess the general processes in place to manage research projects including the quality control system applied to the service foreseen with regard to

- quality of deliverables,
- mechanisms to ensure the committed level of expertise and resources throughout the whole duration of the contract,
- management of agreed timelines,
- strategies to overcome difficulties in meeting deadlines and contingency planning (e.g.in case of absence of a team member),
- policy on conflicts of interest.

14.2. Price

- Only those tenderers which have obtained the stipulated minimum scores for a particular lot shall be evaluated for price and thus for award of a framework contract of that lot.
- Price shall account for **30%** of the weighting for this procurement procedure.
- The award criteria for price shall be evaluated according to the following formula:

$$\frac{\text{Lowest price x weighting for price}}{\text{Tenderer's price}}$$

- For the purposes of evaluation "price" in this formula shall be the grand total for the hypothetical specific service assignment per lot in the appropriate costing sheets in **Annex II.1 to II.4** calculated to two decimal places.

  Tenderers' attention is drawn to Article 151 of the Rules of Application of Regulation (EU, Euratom) No. 966/2012 of the European Parliament and of the Council on the financial rules applicable to the general budget of the Union, as amended, concerning abnormally low tenders.

14.3. Total points for award criteria

Following evaluation of price, the points for the qualitative award criteria and the points for price shall be added together to arrive at a grand total to two decimal places and an overall ranking of tenderers per lot. Up to five framework contracts per lot for lots 1, 2 and 3, and up to eight framework contracts for lot 4 are expected to be signed with the highest ranking tenderers for each lot.