Clinical Trial Unit,

Hospital Pharmacy Central Denmark Region

Letter of Introduction

The aim of this Letter of Introduction is to clarify general guidelines for working with the Hospital Pharmacy Central Denmark Region as a collaborative partner when implementing and managing clinical trials.

Further information can be obtained by contacting:

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Authorisation number for Hospital Pharmacy Central Denmark Region: 395

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1. The Clinical Trial Unit

The Hospital Pharmacy's Clinical Trial Unit (CTU) is the Point of Contact for all initial contacts from investigators, Clinical Research Units, pharmaceutical companies and Clinical Research Organisations (CRO).

The CTU is staffed with employees representing all production and quality departments of the Hospital Pharmacy.

The CTU can be reached by email on weekdays (Monday-Friday).

2. Hospital Pharmacy Central Denmark Region

The Hospital Pharmacy Central Region Denmark (RAM) possesses the necessary authorisations, qualifications and facilities to serve as a professional clinical trial collaborator.

a. Authorisation

According to The Danish Pharmacy Act, RAM is authorised to manufacture and distribute medicinal products (Section 39 Authorisation) adhering to the following legal requirements:

- The Danish Medicines Act
- The Danish executive order regarding medicinal products
- The Danish executive order regarding the manufacture, import and distribution of active pharmaceutical ingredients (APIs) used in the preparation of medicinal products
- The Danish executive order regarding the manufacture and import of medicinal products and intermediary products
- The Danish executive order regarding final preparation of medicinal products in hospital pharmacies
- The Danish executive order regarding the distribution of medicinal products
- Eudralex Vol. 4 – Good Manufacturing Practice (GMP guideline)
- REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC
- ICH Guideline for Good Clinical Practice

All handling of raw materials and investigational medicinal products – including receipt, storage and distribution - is conducted according to current Danish/EU legislation.

RAM is frequently inspected by The Danish Medicines Agency ("Lægemiddelstyrelsen"). Information about date of last inspection can be obtained upon request.
Please see appendix 1 for RAM's "Authorisation to Manufacture and Distribute".

b. Quality Management System

RAM has a quality management system to ensure that all tasks are carried out in accordance with existing legislation.

The computer program "e*D*ok" is used for document management. This program is used to store, distribute and to sign read receipts for RAM's policies, guidelines and SOPs. e*D*ok is an electronic document management system that continually ensures that only the current version of a document is available. No physical copies are available for distribution.

c. Personnel
RAM employs e.g. pharmacists, pharmaconomists, pharmacy technicians, laboratory technicians and service assistants. Personnel with responsibilities regarding clinical trials receive specific training when relevant.

Upon request CVs (curriculum vitaes) and documentation for completed GCP training concerning relevant personnel can be handed out. The Hospital Pharmacy reserves the right to evaluate who is to be considered relevant. This evaluation is carried out when considering each individual clinical trial.

Employees at the Hospital Pharmacy do not necessarily sign documents regarding financial disclosures or confidentiality agreements. Permission to gather, store or distribute personal data is not necessarily given either. The Hospital Pharmacy reserves the right to assess what is considered relevant / reasonable to give consent to.

Employees at the Hospital Pharmacy do not appear on the investigator's delegation log. The pharmacy solves trial-specific tasks per contract and not on the basis of delegation. A trial-specific cooperation agreement (contract) is entered into between the Hospital Pharmacy and the investigator. If the sponsor or investigator requires, a signature log can be drawn up at the Hospital Pharmacy stating the relevant/involved employees and their signature.

d. Services and facilities
RAM provides the following range of services regarding clinical trials:

- Advice and guidance in the planning of clinical trials – e.g. information necessary for the notification form for the Danish Medicines Agency, information on import of medicinal products, blinding, randomisation as well as suggestions for practical and logistical solutions concerning the handling of investigational medicinal products
- Formulate the "sIMPD" (simplified Investigational Medicinal Product Dossier)
- Assessment of stability data (stability testing and/or risk assessment)
- Order, receive and store active pharmaceutical ingredients, investigational medicinal products and relevant utensils – this includes the documentation on import and storage conditions
- To manufacture, reconstitute, prepare, repackage and label investigational medicinal products
- Preparation of randomisation lists
- Blinding of investigational medicinal products
- Dispense and distribute investigational medicinal products
- Accountability logs for investigational medicinal products
- Availability for monitor visits, audits and inspections
- Destruction of investigational medicinal products
- Filing of trial documentation

RAM can provide the following facilities:

- Preparation areas for antibiotics
- Preparation areas for cytotoxics
- Preparation areas for monoclonal antibodies
- Sterile and non-sterile preparation areas for other categories of pharmaceutical products
- Storage facilities for room temperature products
- Storage facilities for refrigerated products (2°C-8°C)
- Storage facilities for frozen products (minus 25°C and minus 80°C, limited capacity)
- Laboratories for physical-chemical and microbiological analysis

Details on monitoring and documentation are described in appendix 2.

Details on the facilities can be obtained by contacting RAM's Clinical Trial Unit (CTU).

Documentation for validation / requalification of facilities, equipment, procedures, etc. is not handed out.

3. Cooperation agreement

RAM will formulate a cooperation agreement for each clinical trial. The agreement is made between RAM and the investigator. RAM does not enter into agreements directly with companies (pharmaceutical companies or CROs).

It is the responsibility of the Investigator to make sure that sponsor is aware of the content and meaning of the cooperation agreement between the Investigator and the Hospital Pharmacy.

Prior to drawing up the agreement, certain documents and information must be made available to RAM. These are listed in appendix 3.

The cooperation agreement contains contact details for all relevant liaisons.

The cooperation agreement defines the services that are to be delivered by RAM. The division of responsibilities between RAM and the investigator (sponsor) is also outlined.

Clinical trials are not part of RAM's basic services and are therefore subject to additional fees. See appendix 5 for a list of services/products that may be associated with a price. The cooperation agreement defines the price for each service and describes the procedures for invoicing.

The cooperation agreement must be finalised and signed prior to first delivery of IMP. In case of substantial amendments during the clinical trials' duration, a new version of the cooperation agreement will be drawn up.

The Hospital Pharmacy reserves the right to invoice "time spent" in connection with trials where time has been spent on start-up, but where the trial is interrupted before signing the cooperation agreement.

4. Start-up agreement

There may be situations where it takes extra time to get a collaboration agreement in place as all preconditions do not exist for finalizing such an agreement. In those cases, a start-up agreement can be drawn up. This is an agreement between the parties about what is to be paid for, regardless of whether the trial is initiated or not.

5. Requirements for sponsor/investigator

For RAM to be able to provide a dependable and satisfactory service there are certain requirements that the sponsors and investigators must fulfil.

These requirements concern the availability of necessary documentation and access to essential information. See appendix 3. This information is necessary to be able to configure the set-up of investigational medicinal products in RAM's production systems.

Please note that it is the responsibility of sponsor/investigator to provide up-to date documentation and information to RAM for the duration of the clinical trial.

If the sponsor chooses to supply a registered drug and refers to the SmPC (Summary of Product Characteristics) instead of referring to an Investigator's Brochure or Pharmacy Manual, it is sponsor's responsibility to monitor changes to the SMPC and to guarantee that any updates to the SMPC are conveyed to RAM.

RAM must be notified and involved as early as possible when planning and initiating a clinical trial. Please invite RAM to preliminary meetings with sponsor/investigator.

6. Production, preparation, dispensing and distribution of investigational medicinal products

RAM makes use of different validated systems for production, preparation and batch documentation. RAM always uses its own validated systems for production, preparation and batch documentation.

All documentation is in Danish. If there is a requirement for translation to another language, the responsibility and cost lies with the sponsor/investigator.

For each clinical trial the specific production system and the format of batch documentation will be indicated in the cooperation agreement.

If the reports provided by IVRS/IWRS or RAM's production systems are not sufficient, RAM can provide drug accountability. RAM reserves the right to use its own forms. These forms can be adapted to each trial.

RAM does not keep empty or opened packaging. Allocated, used or opened packages are discarded immediately after use. Discarding and disposal follows RAM's standard procedures for waste handling (see section 9 in this document).

RAM reserves the right to make demands concerning utensils, infusion solutions etc. to be used in the preparation of the investigational medicinal products. This in consideration of procurement agreements, workstreams and validation of equipment and procedures.

When dispensing or delivering investigational medicinal products, there might be requirements for the receiving party (typically the clinic) to sign for the receipt. In that case the signed document should be sent or e-mailed to RAM. This requirement will be described in the cooperation agreement. It is important to fully comply with this procedure. RAM will not dispense further investigational medicinal products if receipt is not confirmed.

7. Monitoring visits

Monitors are welcome to visit RAM - the CTU and the relevant production departments. RAM must be informed of the monitoring plan prior to site initiation. Actual visits are planned on an ad hoc basis with at least 10 working days' notice.

During the monitoring visits the monitor will have access to agreed data, investigational medicinal products and relevant personnel. Monitor does not gain independent access to electronic production system, but can get access to selected batch documents (samples) accompanied by hospital pharmacy staff. Batch records from the electronic production system may not be printed.

There is a desk and a photocopier available, but monitor must bring their own telephone and computer. Wi-fi is available.

Monitors are not granted access to production areas. Access to storage facilities can be arranged – if so accompanied by hospital pharmacy staff.

8. Audits

RAM participates and should be involved in the planning of audits. This is necessary to ensure that the relevant personnel can be present. Notice must be given at least 20 working days prior to the audit. The final agenda for the audit must reach RAM no later than 5 working days prior to the audit.

9. Receipt of supplies for clinical trials (return of shipping containers, loggers etc.)

Investigational medicinal products and other relevant supplies must be shipped directly to the production department as agreed upon in the cooperation agreement.

Shipments can be delivered to RAM within normal opening hours – Monday-Friday between 08:00 and 15:00. Each shipment must contain the documents necessary to perform receipt and import control. Specific documents will be defined in the cooperation agreement.

If the sponsor demands return of shipping containers, temperature loggers or other equipment, it is the sponsor's responsibility to arrange and pay for their return – this includes submitting return labels and export declaration if relevant. This must be agreed upon when negotiating the cooperation agreement and the arrangement must be evident from the cooperation agreement.

10. Transportation

Investigational medicinal product or other clinical trial supplies can be transported in different ways from the Hospital Pharmacy:

1. Investigator or clinical staff collects the supplies from the relevant production department

2. Use of hospital porter to bring the supplies from the Hospital Pharmacy to the clinic/investigator
3. Clinical trial supplies are transported on the regular runs using MidtTransport (Central Denmark Region's in-house carrier company)
4. Specifically ordered (dedicated) transport using external carrier company
5. Sponsor/investigator has made own arrangements concerning transport. The Hospital Pharmacy hand over the clinical trial supplies to the appointed carrier

The chosen solution for transportation will be clearly described in the study specific cooperation agreement.

When solution 1 or 2 is used, temperature is not logged during transport.

When solution 3 is used, the temperature is logged during transport. MidtTransport is responsible for the logging and notification of RAM in case of temperature deviations. For transports carried out without deviations, RAM is not in possession of the temperature data, given that these data are gathered, monitored and kept by MidtTransport according to the contract between RAM and MidtTransport.

When solution 4 is used, the temperature is logged during transport. The external carrier company is responsible for the logging and notification of RAM in case of temperature deviations. For transports carried out without deviations, RAM is not automatically in possession of the temperature data, but these can be provided for a fee.

When using solution 5, it is the sponsor/investigator's responsibility to make arrangements regarding logging of temperature and access to data.

11. Discarding and disposal

a. Unused investigational medicinal product
RAM can take responsibility for the drug inventory and for the shipment of unused investigational medicinal products to be returned to the sponsor or to destruction. This applies to investigational medicinal products that have not been dispensed from the Hospital Pharmacy.

The drug inventory and the shipment can be documented.

When shipping waste for disposal the actual destruction by incineration can not be documented. The incineration is performed by an external company.

All medicinal waste from RAM's Aarhus and Gødstrup departments is transported for incineration at Fortum Waste solutions A/S in Nyborg. This applies to all medicinal waste.

b. Empty or partly used packages
All medicinal waste from RAM's Aarhus and Gødstrup departments is transported for incineration at Fortum Waste solutions A/S in Nyborg. This applies to all medicinal waste.

c. Unused investigational medicinal product / Empty or partly used packages discarded by the clinic (investigator).

Investigational medicinal products and packaging that are to be discarded and disposed of by the clinic (investigator) are handled the same way as the rest of the clinic's clinical waste. That means according to local procedures valid for the site.

12. Archiving

Documentation is archived for up to 25 years after the completion of the clinical trial. Archiving period depends on the type of documentation and whether the trial has been approved in accordance with Directive 2001/20/EC or Regulation (EU) 536/2014. According to the Regulation, documentation that is part of the trial's Trial Master File must be archived for 25

years. Other documentation (GMP) – including temperature logs – is archived for 5 years. The archiving period and location are specified in the cooperation agreement for each trial.

If it has been agreed that documentation is archived with the sponsor/investigator (GxP environment), the Hospital Pharmacy reserves the right to access the documents for 5 years after the end of the trial. In particular, documents relating to receiving/import control are to be regarded as GMP documents and must therefore be available, e.g. in connection with inspection/audit.

13. Log of changes

Date	***Version***	***Changes***
Jan. 2019	3.0	Log of changes added. Details concerning temperature registration during transport added. Appendix 1a (statement from the Danish Medicines Agency added.
Jul. 2019	4.0	Address corrected. Authorisation number added. Addition regarding investigator's responsibility to make sure that sponsor knows the content and meaning of the cooperation agreement. Addition regarding possible billing of spent time. Elaboration on monitor's access to electronic data. Appendix 1b removed and appendix 1a renamed "Appendix 1". Addition in appendix 3 regarding information on the specific manufacturer of registered drugs used in clinical trials
Jun. 2021	5.0	Changed address. changed time regarding receipts of goods. Minor adjustments and corrections. Appendix 1 – new version of statement. Appendix 3 changed. Added appendix 4 and 5.
Jun. 2022	6.0	Herning changed to Gødstrup. New supplier of waste incineration. Adapted to new EU regulation. Changes regarding temperature monitoring RHG. Appendix 3 adjusted to new procedure for invoicing and added procedure for primary packaging supplied from sponsor.
Jan. 2023	7.0	The Danish executive order regarding final preparation of medicinal products in hospital pharmacies added. Update regarding transportation. Specification regarding archiving.
Jul. 2023	8.0	Paragraph 12 extended regarding archiving.
Nov. 2023	9.0	The Hospital Pharmacy has changed its name in Danish. The English designation is retained except for the abbreviation that changes from HRM to RAM. Paragraph 2c added description regarding delegation. Appendix 1 replaced with new version Appendix 3 expanded regarding required documentation for authorisation through CTIS.

Appendix 1 – Manufacturing and import authorisation

LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

Regionsapoteket Midtjylland
Klinisk forsøgsenhed
Universitetsbyen 30
DK-8000 Aarhus C

Date: 26.09.2023

Statement concerning manufacturing authorization

Pursuant of the Danish Pharmacy Act, hospitals pharmacies in Denmark have an inherent permission to manufacture medicinal products.
Hospital pharmacies are therefore not issued an official manufacturing authorization by the Danish Medicines Agency.

This statement is to confirm that the hospital pharmacy "Regionsapoteket Midtjylland" has legal permission to manufacture medicinal products including investigational medicinal products.
The hospital pharmacy is also permitted to receive imported medicinal products including investigational medicinal products and medicinal products for compassionate use.

Best regards

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Appendix 2 – Hospital Pharmacy facilities – monitoring and documentation

a. Temperature monitoring

In all locations (storage rooms, cold rooms, refrigerators) where medicinal products are stored the temperature is logged.

Where possible this is done by using CTS (CTS = BMS = Building Management System) or FMS (Facility Monitoring System).

In locations where CTS/FMS is not an option, external loggers ("MicroLite" and "Testo") are used.

CTS/FMS sensors and external loggers are re-validated yearly.

The departments of RAM are each responsible for the temperature monitoring. In each department one person has been appointed responsible for the task.

Temperature monitoring using CTS

CTS-sensors register the temperature continuously and log the temperature at least every 10 minutes.

If the CTS system detects that the temperature has been outside the limit for a longer period of time, an alarm is activated at the Technical Support Department. For refrigerators, freezers and cold rooms, the alarm is activated after exceeding for 20 minutes and for room sensors / production rooms after 40 minutes. As the temperature is registered continuously, the alarm can also be activated between data logs.

During RAM's opening hours the Technical Support Department contacts the pharmacy department where the alarm has been activated. The department is responsible for corrective measures, relocating and quarantining the stock if necessary and the case management regarding the temperature deviation.

Outside opening hours, the Technical Support Department contacts the pharmaconomist on duty or the relevant supervisor, who will then see to the corrective measures, relocating and quarantining of stock if necessary as well as assigning the case management regarding the deviation to the relevant party on the next work day.

At regular intervals the pharmacy departments print data files showing the logged temperatures for the past period of time.

If any readings are outside the acceptable temperature range, the person responsible makes an assessment of the data. If the duration of the temperature excursion is less than 20 minutes / 40 minutes, the excursion is documented on the print-out by recording the cause (e.g. when medicinal products are put into stock), signing and dating the document. In the event of temperature excursions longer than 20 minutes / 40 minutes, a deviation report will be completed.

Temperature monitoring using ViewLinc FMS (Facility Monitoring System)

The temperature is monitored by sensors/loggers connected to a dedicated server. The ViewLinc software stores data electronically. Data is logged every minute by validated and calibrated loggers.

If the FMS system detects that the temperature has been outside the limit for a longer period of time, an alarm is activated at the Technical Support Department. For refrigerators, freezers and cold rooms, the alarm is activated after exceeding for 20 minutes and for room sensors / production rooms after 40 minutes. As the temperature is registered continuously, the alarm can also be activated between data logs.

During RAM's opening hours the Technical Support Department contacts the pharmacy department where the alarm has been activated. The department is responsible for corrective measures, relocating and quarantining the stock and documenting the temperature deviation.

Outside opening hours, the Technical Support Department contacts the pharmaconomist on duty or the relevant supervisor, who will then see to the corrective measures, relocating and quarantining of stock if necessary as well as assigning the case management regarding the deviation to the relevant party on the next work day.

At regular intervals the pharmacy departments print data files showing the logged temperatures for the past period of time.

If any readings are outside the acceptable temperature range, the person responsible makes an assessment of the data. If the duration of the temperature excursion is less than 20 minutes / 40 minutes, the excursion is documented on the print-out by recording the cause (e.g. when medicinal products are put into stock), signing and dating the document. In the event of temperature excursions longer than 20 minutes / 40 minutes, a deviation report will be completed and sponsor/monitor notified.

Temperature monitoring using external "MicroLite" logger

- Data is logged every 15 minutes
- The logger is manually checked (no printing) at least once a week to see, if there has been any excursions since the last check.
- If the outside temperature exceeds 25 ºC, the check is performed daily during the working week.
- Data from the logger is downloaded to a computer and the temperature logger is reset every 3 months. Data is filed on RAM's network drive.

If temperature excursions are observed during the weekly check, the data from the logger is downloaded and the logger is reset. The observed excursion is assessed by the person responsible for the department's temperature monitoring. A deviation report is prepared and relevant corrective measures are implemented.

Temperature monitoring documentation (CTS, FMS and external loggers)

Documentation consists of printed graphs. These are filed by the individual departments.

In case sponsor wishes trial specific archiving of temperature records, it is the responsibility of the clinical trial monitor to make paper copies of the documentation and file these in the study files.

b. Environmental monitoring

In compliance with GMP and RAM's standard operation procedures the microbiological environment is monitored at fixed intervals using validated methods.

The following methods are used in RAM's environmental monitoring program.

Microbiological testing:

- Agar plates with disinhibitor for gloves/hands
- Agar plate (settle plates) with disinhibitor for air. Passive sampling.
- Contact plates with disinhibitor for surfaces, equipment and clothing
- Swab sampling for surfaces and equipment
- Volumetric air sampling

Other methods:

- Particle counting

GMP guidelines do not specify any special requirements for rooms used to manufacture non-sterile medicinal products and thus no special requirements for the environmental monitoring. Based on the GMP guidelines definition of grade D rooms, RAM has established a programme for monitoring the environment in rooms where the preparation of non-sterile medicinal products is carried out.

c. Access

Access to buildings, rooms and storage facilities is limited according to the standard operating procedures of RAM. Only employees have access to production rooms, storerooms, cold room, freezers and refrigerators.

Appendix 3 – Check list

The following documents and information must be forwarded to RAM (Hospital Pharmacy Central Denmark Region) prior to the negotiation and conclusion of the cooperation agreement.

Please note that some points are only relevant if trial specific Investigational Medicinal Products (IMPs) are used. These are marked with a "**X**".

Documents

1. Protocol, current version.
2. Amendments (if applicable).
3. Protocol summary in Danish (if applicable).
4. **X** Investigator's Brochure(s).
5. **X** Pharmacy Manual/Drug Handling procedure/Summary of Product Characteristic (SMPC) or equivalent detailed description of the handling of all IMP's.
6. IxRS-manual (if applicable).
7. Approval from relevant authorities. Must contain documentation of:
   - authorisation in Denmark
   - date for "Estimated end of trial"
   For Clinical trials authorised through CTIS pdf-version of *Initial PART I* and *Final Assessment Report* must be sent to the Hospital Pharmacy
8. **X** Manufacturing Authorisation or Wholesale Dealer Authorisation for the manufacturer (responsible for batch release)/distributor of IMP.

Supplies/logistics

9. **X** List of all IMPs supplied by sponsor. Please state all trade names, generic names, administration form and pack size.
10. List of all IMPs where RAM must use registered medicinal products from stock. Please state all trade names, generic names, administration form and pack size.
11. **X** List of all utensils, labels and/or other materials supplied by sponsor. Please specify what is supplied and where/when it is to be used.
12. List of all utensils, labels and/or other materials where Hospital Pharmacy must use goods from own stock. Please state all trade names, specifications and where/when it is to be used.
13. **X** Procedure for ordering IMP - e.g. IWRS/IVRS, Hospital Pharmacy to manage stock and place orders through usual vendor, order by e-mail to monitor/sponsor?
14. **X** From which company and address is the IMP shipped?
15. **X** Who (what company) issues the release certificates? Address must be specified.
16. **X** How must receipt be acknowledged? IxRS or by e-mail?

17. **X** How often will IMP be delivered?

18. **X** How many packages does each shipment contain?

19. **X** Will there be an initial shipment? What does it contain and when/how is it triggered?

20. **X** Must shipping boxes be returned?

21. **X** Will IVRS/IWRS be used for allocation of IMP to patients? Specify what activities the Hospital Pharmacy is to carry out in the IWRS.

Contacts

22. Investigator (sub-investigator) (title, name, clinic, address, phone no. and e-mail).

23. Study nurse (title, name, clinic, address, phone no. and e-mail).

24. Sponsor (company/clinic, title, name, address, phone no. and e-mail).

25. Person responsible for finance (title, name, address, phone no. and e-mail).

26. Supplier of IMP (company, title, name, address, phone no. and e-mail).

27. Monitor (company, title, name, address, phone no. and e-mail).

28. Debtor and FAS no. if applicable. Alternatively, information necessary to set up a trial specific debtor (specified when drawing up the cooperation agreement).

29. Monitoring plan (as detailed as possible on monitoring interval, expected duration of visits, which hospital pharmacy personnel should be present and specification of what data/documentation the monitor needs access to).

Miscellaneous

30. Are there other tasks which RAM is expected to fulfil?
    If "Yes", please specify/describe in detail.

If required by RAM, the data listed below must be made available to RAM well in advance of dispensing of first dose to the first patient.

Master data

31. **X** Specific density of liquid formulations (stated in g/ml and valid for the temperature at which the IMP must be handled).

32. **X** Surplus of active substance (solid/lyophilize).

33. **X** Amount (weight) of excipients (solid/lyophilize).

34. **X** Concentration of active substance after reconstitution.

35. **X** Stability after opening.

36. **X** ATC-code (if known).

PLEASE NOTE!

Regarding investigational medicinal products supplied from sponsor, it is the responsibility of the sponsor to guarantee that all documents required are the up-to-date versions and that they are made readily available for RAM for the duration of the clinical trial.

The sponsor is responsible for monitoring any changes to the published SMPC and for informing RAM of any changes concerning the investigational medicinal products in use.

Regarding investigational medicinal products where RAM uses registered products from stock, monitoring changes of SmPC's is part of the standard procedures undertaken by RAM. It also applies that the registered/marketed drug products used are determined by an EU invitation to tender. Specific manufacturer/supplier depends on the current tendering period and can be provided on request.

Study specific packaging – demands and responsibilities

If sponsor determines and delivers packaging for use in a specific trial, the sponsor is responsible for the specifications, suitability, compatibility and physical-chemical stability of the trial drug in the specific packaging.

If necessary, the Hospital Pharmacy performs an integrity test and assesses whether handling/ use of the packaging is covered by the pharmacy department's microbiological validation (substrate filling).

The Hospital Pharmacy reserves the right to reject the use of specific packaging if this can compromise the environment or work processes.

Appendix 4 – Source data list

- Prescription/ordering of IMP
  - Serviceproduktion Aarhus and Regionshospitalet Gødstrup (RHG)
    Order form mailed from investigator to Serviceproduktionen.
    Stored in Trial file / Pharmacy binder.

  - Cytostatikaproduktion Aarhus and RHG
    - ◊ Prescription/ordering performed in "Kompleks medicinering" (electronic patient record). Stored electronically.
    - ◊ Prescription/ordering sent by "scan to folder" or mail).
    - ◊ Stored in relevant production department.

  - Produktion Skejby
    Order form mailed from investigator to Produktion Skejby.
    Stored in Trial file / Pharmacy binder.

- Preparation forms
  - Serviceproduktion Aarhus and RHG
    "Hovedforskrifter". Printed from current version of *e*Dok prior to the manufacture of each batch.

  - Cytostatikaproduktion Aarhus and RHG
    Manufacture/production is managed, guided and documented using the electronical production system CATO.

  - Produktion Skejby
    Manufacture/production is managed, guided and documented using the electronical production system CATO.

- Batch documentation
  - Serviceproduktion Aarhus and RHG
    Batch documentation is stored in Trial file / Pharmacy binder.

  - Cytostatikaproduktion Aarhus og RHG
    Batch documentation is stored electronically and when relevant as paper copies (volumetric or manual production) in relevant department.

  - Produktion Skejby
    Batch documentation is stored electronically and when relevant as paper copies (volumetric or manual production).

- Drug accountability
  Stored in Trial file / Pharmacy binder.

- Temperature logs
  - Hospital Pharmacy departments placed at Universitetsbyen, Aarhus
    Print of CTS-data is stored in paper copy in the department responsible for the storage facility in question.
  - Hospital Pharmacy departments placed at Regionshospitalet Gødstrup
    Print of FMS and logger data stored in paper copy.

  - Hospital Pharmacy departments placed at Aarhus University Hospital
    Print of CTS-data is stored in paper copy in the department responsible for the storage facility in question.

- Documentation regarding receipt and import at Hospital Pharmacy
  Stored in Trial file / Pharmacy binder.

- Delivery of IMP to investigator and receipt for delivery from investigator
  Stored in Trial file / Pharmacy binder. (If applicable)

- Destruction of IMP
  Stored in Trial file / Pharmacy binder.

- Training logs
  Logged in *e*Dok. On request printed and stored in Trial file / Pharmacy binder.
  Manually signed logs are stored as paper copies in Trial file / Pharmacy binder.

- CV's
  Delivered on request. If the sponsor / monitor wants a copy in the Trial file / Pharmacy binder, it is the sponsor's/monitor's responsibility to see to this. CVs are not updated at fixed intervals but only when there are changes.

- GCP Certificates
  Delivered on request. If the sponsor / monitor wants a copy in the Trial file / Pharmacy binder, it is the sponsor's/monitor's responsibility to see to this. GCP Certificates are not updated at fixed intervals.

- Randomisation, IRT-prints
  Stored in Trial file / Pharmacy binder.

- Note to File (NTF)
  Stored in Trial file / Pharmacy binder.

- Deviation Reports and Change Controls
  Stored electronically in FileMaker.
  On request printed and stored in Trial file / Pharmacy binder.

Date:_____

Signature (monitor/sponsor):_____

Bilag 5 – Services/products that may be associated with a price

- Start-up fee. (Billing per hour. For commercial trials the number of hours charged depends on the scale and complexity of the trial. Investigator initiated trials are charged for 10 hours.)
- New version of the cooperation agreement necessitated by changes made by sponsor or investigator. (Billing per hour.)
- Advice on legislation regarding IMP. Depends on scope and context. (Billing per hour.)
- Teaching/training, e.g. regarding additional labelling. (Billing per hour.)
- Receipt of IMP (e.g. documentation of receipt/import from foreign country, fulfilling specific demands from sponsor/supplier regarding forms, loggers or shipments missing the necessary batch documentation). (Billing per hour.)
- Manufacture of IMP (raw materials, packaging, labels, time, utensils).
  Price is calculated for 1 package or for a fixed number of packages manufactured and delivered at the same time.
- Preparation of IMP (drug products, packaging, labels, time, utensils).
  There is a fixed fee per unit when preparing cytotoxics, antibodies and antibiotics for named patient.
  For other products a price is calculated for 1 package or for a fixed number of packages manufactured and delivered at the same time.
- Repackaging/labelling/additional labelling of IMP.
  There is a fixed fee per unit when preparing cytotoxics, antibodies and antibiotics. For other products a price is calculated for 1 package or for a fixed number of packages manufactured and delivered at the same time.
- Extension of expiry (re-labelling) of IMP. (Billing per hour.)
- Storage of IMP (depending on amount and storage facility).
- Preparing delivery of IMP to investigator or patient. (Billing per hour.)
- Transportation of IMP. Depends on chosen solution for transport.
- Transfer of IMP to another site. (Billing per hour.)
- Return of IMP to sponsor. (Billing per hour.)

- Return of shipping boxes and/or temperature loggers to sponsor/supplier. (Billing per hour.)
- Monitor visits/audits. Time spent with monitor/auditor. (Billing per hour.)
- Changes to IMP (e.g new manufacturer, new administration form, new package size). (Billing per hour.)
- Generating randomisation list and code envelopes. (Billing per hour.)
- Generating AB-lists. (Billing per hour.)
- Time spent on fulfilling special requirements from sponsor/investigator (e.g. activities in IxRS, eCRF when receiving, allocating or destroying IMP). (Billing per hour.)
- Time spent on fulfilling special requirements from sponsor/investigator (e.g. time spent issuing certain calibration certificates. (Billing per hour.)
- Storage/archiving documentation for longer than required by law. Price depends on amount and duration.
- Extraordinary accounting for IMP. (Billing per hour.)
- Cancellation of IMP after started or completed preparation/manufacture.
- Drug products, packaging, utensils or other material sourced specifically for a clinical trial but not used.
- Issuing of certificates – e.g. QP Certificates. (Billing per hour.)

Hourly rate is regulated approximately once a year - typically in January. The current hourly rate can be provided on request.