## **SPECIFICATION: DETAILS OF REQUIREMENTS**

Specification for the delivery of Investigational Medicinal Products for IMPEDE-PKD drug trial.

## Atamis Reference Number: C289889

## Deadline for receipt of Tenders to be received: 27/08/2024 13:00

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##### Trial Title

Implementation of Metformin therapy to Ease Decline of kidney function in Polycystic Kidney Disease (IMPEDE-PKD) Randomised Placebo-Controlled Trial (NIHR156614)

##### Trial Objectives

To evaluate the long-term efficacy of metformin therapy in slowing the rate of kidney function decline in metformin versus placebo treated autosomal dominant polycystic kidney disease participants.

##### Sponsor

Sheffield Teaching Hospitals (STH)

##### Coordinating Centre

Norwich Clinical Trials Unit (NCTU)

##### Trial Design

Pragmatic, multi-centre, double-blind, parallel group randomised controlled trial of metformin versus placebo in ADPKD patients.

##### Participants

300 participants with Autosomal Dominant Polycystic Kidney Disease (ADPKD). These participants will be recruited from 35-40 NHS Trusts

##### Interventions

Participants randomised to the interventional arm will receive a once daily extended release (ER) metformin preparation between 1000mg-2000mg based on the maximum dose tolerated. ER preparations have slower gastric absorption, reaching peak plasma concentrations at 7 hours (IR preparations = 3 hours). They are therefore associated with reduced gastrointestinal symptoms and coupled with once daily administration this provides improved compliance.

Participants randomised to the control arm will receive a matched placebo.

##### Randomisation

Randomisation will be performed by NCTU and the global sponsor and will allocate participants to either active Metformin arm or the matched placebo control (1:1)

##### Dose Titration

All participants will undergo a 12-week metformin run-in, commencing 1000mg daily. This will be titrated up every 4 weeks to the maximum tolerated dose (not exceeding 2000mg). This process will happen before they start the double-blind trial.

NB this drug will be provided by local sites from hospital stock and use an Annex 13 exemption. As a result, the drug for the run-in phase has been excluded from the requirements in this bid.

##### IMP Requirements

* Product:  Metformin XR 500mg tablets.
* Product: Placebo identical in appearance and packaging to the Metformin XR 500mg tablets.
* The contractor to purchase or manufacture Metformin XR 500mg tablets aiming for a shelf life of 2+ years.
* The Placebo tablets must have a shelf-life matching that of the Metformin XR 500mg tablets.
* Daily Dose:  2000mg daily, target dose, minimum dose 1000mg daily in case of intolerance (assume that all patients will tolerate 2000mg daily)
* Trial IMP to be available from 01/10/2024 to 31/10/2028.
* Recruitment period for participants 24 months (c. 01/10/2024 – 31/10/2026)
* Treatment length for each participant:  24 months (End of Treatment, last patient c. 31/10/2028)
* Dispensing frequency: 6 monthly.
* Pack size:  128 tablet bottles/blister packs packed into kits of 3 bottles/blister packs per kit.  Each participant will need 8 kits in total (24 bottles/blister packs)
* Number of participants in the UK:  300 randomised, recruitment period:  24 months.  =   1200 kits of placebo and 1200 kits of Metformin = 2400 kits plus necessary overage.
* Initial purchase will be for 20% of the total quantity of metformin and placebo. Future purchases dependent on the outcome of the internal pilot study.
* Number of sites: 35-40 UK sites proposed. Deliveries to be made direct to site pharmacies and to be covered by relevant temperature monitoring as appropriate for the product. Estimate 2 deliveries per site per production run.
* Blinding:  Full blinding of IMP packs required. Packs to be identified with pack-specific IDs to allow pack allocation by an external globally managed IWRS system.
* Simplified IMPD(s) and IMP labels required for regulatory submission during trial set up period and within 4 weeks of contract award.
* Minimum of 4 production runs (will depend on achievable shelf-life and taking into account a built-in stop/go milestone at the end of the internal pilot period).
* If The bidder plans to sub-contract any of the manufacturing services these must be expressly agreed in the contract or Technical Agreement with Sheffield Teaching Hospitals; and in any event the contractor shall remain responsible to Sheffield Teaching Hospitals at all times for the proper performance of the services by its sub-contractors.
* The bidder must be able to produce data to support the shelf life of the placebo production and packaging within the timelines required by the project.

##### Certification, Qualifications, Competencies Training and Policy Requirements

* The bidding organisation must be a holder of, and supply a copy of, an MIA(IMP) license appropriate to the activities required for the manufacture of IMP and placebo required by this project.
* The bidding organisation must be able to provide simplified-IMPD documentation for the IMP and placebo.
* The bidding organisation must be able to provide QP certification for the IMP and placebo for release of product for human use within the UK.
* The bidding organisation must be able to provide appropriate analytical and stability testing to comply with requirements for QP UK release criteria.
* The bidding organisation must be able to manage the project and documentation pertaining to the project to standards as laid out in UK GMP and GCP legislation.

##### Trial Summary

Once the contract is awarded, The bidder must produce simplified-IMPD documentation within 4 weeks and supply to Sheffield Teaching Hospitals along with IMP labels and all relevant certificates required for MHRA and Ethics approval.

Sheffield Teaching Hospitals will then commence the recruitment of trial participants and the initial 12 weeks metformin run-in.

The expectation is that 300 participants will be recruited to the trial.

Each participant will take either 4 tablets of Metformin XR 500mg or the placebo.

The tablets to be packaged into bottles/blister packs of 128 tablets.

The bottles to be supplied as kits of 3 bottles/blister packs.

1200 kits, 3600 bottles/blister packs, 460,800 tablets, each of Metformin XR 500mg and a placebo, will be required throughout the trial if 300 participants are recruited-Plus necessary overages (please note that clarification on how many overages are required will form a question in Supplier Tender Return)

The bidder should begin the process to prepare 240 kits each of the Metformin XR 500mg and placebo, once MHRA approval has been confirmed, to be ready for distribution to the participating Trusts in advance of the first participants reaching the end of their run-in period.

##### Purchase or Production of IMP and Placebo

* Once MHRA approval has been granted, the bidder will begin production of Metformin XR 500mg and a matching placebo.
* The initial purchase will be for 20% of the total quantity of Metformin XR 500mg and placebo.
* The bidder must purchase or manufacture Metformin XR 500mg aiming for a shelf life of at least 2 years.
* The bidder must manufacture a matching placebo, identical in appearance to the Metformin XR 500mg.
* The shelf life of the Placebo tablets must at least match that of the Metformin XR 500mg
* Any sub-contracting of manufacturing services must be expressly agreed in the contract with Sheffield Teaching Hospitals; and in any event The bidder shall remain responsible to Sheffield Teaching Hospitals at all times for the proper performance of the contract.
* The bidder must be able to produce data to support the shelf life of the placebo production and packaging.
* If The bidder has a process to allow for shelf-life extension, up to the maximum allowed for the product, if the full shelf life is not assigned initially, details must be confirmed in the contract.

##### Storage

* The bidder must be able to purchase, accept and store bulk shipments of active drugs from raw material manufacturers. There may be up to five bulk deliveries of the IMP.
* Trial stock must be stored in line with the requirement of each product.
* Trial stock must be stored in a facility with appropriate environmental and temperature monitoring covering a period up to 31/10/2028, with the ability to accommodate any agreed extension if required.
* Any temperature deviations (of raw product or packaged trial stock) during storage must be reported to STH/NCTU.

##### Packaging for the blinded trial

* After the initial order as detailed in the trial summary, further campaigns will be run in accordance with the requirements of the trial and in consultation with STH and NCTU.
* Tablets must either be counted into child-resistant, tamper-evident bottles or packed into suitable primary blister packs and secondary packaging for each of the IMPs
* The appearance of the Metformin XR 500mg tablets and the placebo must be identical
* The packaging for the Metformin and placebo must be identical.
* Bottle/blister pack size must be 128 tablets and these should be packaged into kits of 3 packs. The total number of tablets/packs/kits is detailed in the trial summary.
* All bottles/blister packs from the same packaging and labelling campaign must be labelled with the same expiry date i.e. using the expiry date from the product with the earliest expiry date.
* The bidder must retain a sample of bottles/blister packs for each IMP in accordance with current regulations and make these available to STH/NCTU upon request to enable product identity confirmation testing if required.
* The bidder must keep a record of batch numbers and expiry dates used for each bottle/blister pack and will supply this in an agreed format to STH/NCTU.
* The bidder must prepare a packaging and labelling batch record for each batch of the product.
* The bidder must keep all original packaging and labelling batch records documentation for a minimum of 25 years.
* The bidder must provide Sheffield Teaching Hospitals NHS Foundation Trust STH) & Norwich Clinical Trials Unit (NCTU) with any corresponding batch documentation as agreed in the technical agreement.
* The bidder must provide a simplified Investigational Medicinal Product Dossier (sIMPD) to support placebo manufacture and stability of active drugs and matching placebo within 4 weeks of the contract being signed.

##### Labelling

* The bidder must create an Annex 13 compliant label (English language only) for primary packaging as agreed by both parties with text provided by STH/NCTU within 4 weeks of the contract being signed.
* The bidder must apply the agreed Annex 13 compliant label with a product identifier to each bottle, upon agreement from STH/NCTU that labelling may commence -this will usually be after regulatory approval of the label.
* The bidder must have the capacity to re-label for expiry date extensions throughout the contract period if required.

##### Qualified Person (QP) Release

* The bidder must have capacity for Qualified Person (QP) certification of packaged and labelled trial drug in line with UK requirements.
* The bidder must provide QP certification to NCTU for the finished products in line with UK requirements prior to distribution.
* Once QP certification has been performed The bidder must notify NCTU of the bottles that have been released and are available for dispatch to sites.

##### Distribution

* The bidder must have the ability and capacity to distribute IMP to approx. 35-40 NHS Trust sites within the UK over a 50-month period according to recruitment rate and in coordination with NCTU. The number of sites may increase or decrease depending on the needs of the trial.
* The bidder must provide temperature-controlled shipping to NHS sites using the most cost-effective method.
* The bidder must have the capacity to distribute the first shipment to NHS sites within 12 weeks of Sheffield Teaching Hospitals confirming MHRA approval.
* The bidder must have appropriate distribution systems and agreements in place to be able to distribute drugs to site within 5 working days of receipt of a drug order request and produce SOPs for these processes.
* The bidder must be able to make approximately 8 deliveries per site in total. The number of deliveries may increase or decrease depending on the needs of the trial.
* Upon order request the bidder must pack the required bottles specified by NCTU and provide confirmation of dispatch to NHS sites, to NCTU via a method to be agreed with NCTU.
* Proof of delivery must be made available upon request.
* The bidder must arrange replacement of damaged shipments/bottles received at site pharmacy and resupply with bottles and will be responsible for covering any cost associated with this.
* All shipments must include a Packing Note confirming each bottle included and QP release for each.
* Should the need to recall trial treatment arise from advice from the manufacturer, supplier or the Sponsor, the bidder must assist NCTU in determining all bottles affected and assist with recall in a timely manner.

##### Performance Standards

* The bidder must provide a defined, experienced Project Manager and/or Local Account Manager for day-to-day operations, query resolution and end-user contact
* The bidder must provide evidence of cover to be provided in the designated project manager/local account managers absence and handover procedures.
* The bidder must perform the project under the terms of a contract which will be set up and agreed between Sheffield Teaching Hospitals and the bidder prior to any work being undertaken, with this technical specification providing the basis for the contract.
* The bidder must be able to grant access to staff from Sheffield Teaching Hospitals and/or NCTU to conduct audit and inspection of its manufacturing facilities related to the product under contract at an agreed time, if such is requested.
* The bidder must hold and provide copies of specific licences, including MIA(IMP) for the manufacture of investigational medicinal products. Copies to be requested from the successful bidder only.
* If the manufacturing licence is renewed during the course of the contract period, copies of the renewed licences must be provided to STH/ NCTU.
* The bidder’s premises must hold and provide copies of specific licenses as required by the competent authority for the activities concerned. The primary license is the MIA(IMP), which must include Manufacturing Operations authorisation which must authorise the company to do the processes which it proposes to use to deliver the service.   Copies to be requested from the successful bidder only.
* The bidder must hold and provide copies of specific licences as required for the import of licenced medicinal products from the EEA (if applicable). The primary license, where the company proposes needing to import to fulfil the service, is the MIA(IMP), which must include an Importation of Medicinal Products authorisation which must authorise the company to do the importation processes which it proposes to use to deliver the service.
* The bidder must ensure that full comprehensive training is provided for handover for QP in the event of absence or change in QP.
* Copies of the QP certification must be provided to STH/ NCTU throughout contract period.
* The bidder must work in accordance with Good Manufacturing Practice (GMP) derived from “the rules governing medicinal products in the European Community, Good Manufacturing practice for Medicinal Products”.
* The bidder must work in accordance with Good Distribution Practice (GDP).
* The contractor must provide ongoing QP advice and guidance for the project including use of products which may have been subject to temperature excursion or other storage deviation at any stage in the life of the product.
* The contractor must work in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments and future relevant revisions, guidelines on Good Manufacture Practices (Volume 4) and Good Distribution Practice.
* The contractor must work in accordance with current European/UK regulations and specifications as agreed in the Technical Agreement between STH and the contractor.
* The contractor must have understanding of and comply with all International (central and regional) legal and regulatory requirements including customs requirements if any part of the work is being performed outside the UK.
* The contractor must have appropriate insurance in place

##### Performance and Contract Management

* The Trust will require a minimum of an annual contract management meetings to review the bidder against the Key Performance Indicators (KPIs) for this contract and discuss matters arising generally under the contract. These meetings are to be held either on site or virtually through MS Teams, to be agreed between the Trust and supplier.
* The bidder must provide a named contact to be the primary point of contact for contract management queries
* Additional contract management meetings may be required if service levels fall below the target detailed in the KPI’s. Action plans to remedy must be agreed with the Trust.
* KPIs can be reviewed and amended or added to at any time with mutual agreement between the Trust and the bidder

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| KPI[ | Method for KPI measurement | Target achievement for KPI | Frequency |
| Bidder to hold valid certificates, as outlined in the Performance Standards of the specification for the duration of the contract. | Supplier presentation  | 100% | Quarterly |
| Bidder to supply medications with expiry dates required in specification. | Management information  | 95% | Quarterly  |
| Bidder to maintain appropriate environment and temperature for storage of medications. | Management information  | 95% | Quarterly |
| Delivery of medications to match requirements of each site  | Management information of recalls  | 95% | After each request |
| Reduction in the use of single-use plastics used in packaging and products | Supplier presentation | Continued reduction | Quarterly |
| Reduction in the Freight miles used to deliver this contract | Supplier presentation | Continued reduction | Quarterly |

##### Complaints Management

Any complaint from sponsor regarding quality of supplied product must be acknowledged by bidder within 2 working days.

A report containing details of the investigation with corrective and preventative actions must be forwarded to sponsor within 30 working days. The Bidder must make every effort to complete investigations and provide feedback including actions assigned to Sponsor in a timely manner.