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BM1105 CLINICAL GROUP LEADERS MEETING MINUTES
June 29th-30th, 2014
Institute of Child Health, London, UK

MEETING OVERVIEW

The meeting objectives included the following items pertaining to the Action deliverables and milestones as stated in the Memorandum of Understanding (MoU)

1. Review Charter for using COST phenotype database (deliverable - patient registry)
2. Consensus statement on evaluation & treatment of CHH (deliverable – guidelines)
3. Discussion of Action-wide protocol, i.e. multi-site international study (deliverable – industry collaboration)

Working Group 1 Objectives (MoU) were reviewed

1. Develop Registry / Database
   - Identify phenotype ontologies to establish consensus for database (i.e. the minimal data set [MDS]) - completed
   - Establish & curate web-based patient registry /collaboration platform – ongoing
   - Enroll patients into registry - ongoing
   - Elucidate patient phenotype-genotype correlations (with WG2 - Genetics) – to be done

2. Website
   - Create and publish guidelines for evaluation & treatment (consensus statement) – in process
   - Establish guidelines for genetic counseling (with WG - Genetics) – revised deliverable (see Annual Progress Report 2)
   - Compile list of specialized referral centers for website – achieved
   - Develop patient-oriented education/advocacy materials for the website (with WG5 – Patient Advocacy) → meeting August 18 to finalize

Working Group 1 Deliverables(MoU) were reviewed

- Publish list of specialized clinical & research centers on the website – achieved
- Harmonize phenotypic definition & structure data collection (MDS) – achieved
- Develop patient-oriented education/advocacy materials (website) – to finalize August 18
- Create clinical guidelines for evaluation & treatment of CHH (i.e. consensus statement) – in process

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Sunday June 29th

Phenotyping Sheet (MDS)
The patient phenotyping sheet (MDS) was reviewed. Members were in agreement that the form was in its completed state and ready for circulation and use. Anders Juul suggested that definitions for diagnoses be provided to ensure coherent, consistent use be used.

- The definition of the diagnosis has been added to the MDS as a "hover function" (i.e. pop-up definition on the pdf form) is not possible
- PDF will be circulated Action wide for entry of patients into the database
- Investigators will be asked to submit 5 patients each in an initial step

Charter for Accessing Database
Based on the work performed at prior meetings (Paris, Lille & Berlin) the Charter was reviewed and discussed.

- Discussion was focused on anonymization issues (i.e. anonymous data vs. de-identified/reversibly anonymized samples)
- Charter was edited line by line and decisions were made regarding the review process, possibility for rebuttal, and issues regarding access to and removal of data (see revised charter circulated to COST Action members July 2014)
- It was emphasized that the database is a research infrastructure for COST participants (with hosting and technical support provided by the Chair's institution - CHUV).
- At the end of the COST grant additional sources of funding will be sought to help support the patient registry as an ongoing research infrastructure (i.e. European Society of Endocrinology)
- It was decided that consent templates will be made available for investigators wishing to develop consent documents for local approval

Consensus Statement for the Evaluation and treatment of CHH
Per the MoU one of the proposed deliverables was to develop a consensus statement representing the agreed upon gold-standard for diagnosis and treatment of CHH.

- The idea of submitting a Nature Reviews Endocrinology paper on clinical aspects of CHH was put forth. Given length limitations, another option was to propose a consensus statement for the European Journal of Endocrinology on diagnosis and treatment.
- The group developed an outline and abstract that will be submitted to Nature Reviews for consideration. If accepted the manuscript will be drafted and circulated to the Clinical Working Group and Working Group leaders for input and comment.
- The groups divided into teams to draft detailed outlines for an expanded consensus statement. The idea being that the outline will be approved then paper drafted followed by open period for comment and input from the Clinical Working Group.

Action-Wide Protocol and Liaison with Industry
As delineated in the MoU, one aspect of the Action will be to work to develop links with industry to accelerate discovery and enhance the translation of research findings into novel approaches for diagnosing, treating, and counseling patients with CHH. As CHH is rare, the notion of developing a protocol evaluating the optimal fertility induction and puberty induction regimes was proposed.

- Nelly Pitteloud provided and overview of the FSH pre-treatment protocol published in JCEM in 2013; 98(11):E1790-5.
- An agreed upon scientific question was to determine the optimal treatment induction regimen i.e. pre-treatment with FSH followed by combined FSH+hCG therapy vs. standard therapy (FSH+hCG therapy)
- Inclusion criteria: 18+yrs, CHH or CPHD with/without crypotrchidism, no prior gonadotropin therapy, TV<4mL, serum T <2nmol/L, BMI>35,
- There was lengthy discussion regarding having patients stop testosterone prior to study enrollment which poses particular challenges for those on Nebido (long-acting testosterone

undecanoate injections). For instance, those on Nebido would have to transfer to a gel approximately 1 year in advance to be able to have an adequately short enough washout to meet the inclusion criteria of testosterone < 2 nmol/L

- Discussion included potential use of long-acting FSH Enlonva (a long-acting purified FSH) if such a formulation was used it would include FSH administration every 2-weeks.
- It was agreed that a target FSH range would be 4-8 U/L and that assays would be done locally with an aliquot banked for end of study analysis. It was proposed that dose adjustments be centralized
- Tesosterone will be measured by M-S, local measurements will be used for dose adjustment with a target trough in the range of 8-15 nmol/L using either 1'000 U 3X/wk or 1'500 U 2X/wk
- Primary endpoints: testicular volume, sperm positive, men attaining 1.5 million/mL, men achieving 15 million/mL
- Secondary endpoints: pregnacy as a successful outcome
- The number of study arms must be finalized as well as . The three possible arms include: i) hCG+FSH, ii) FSH long-acting (Q 2wks) → hCG+FSH, iii) FSH (75IU every other day) → hCG+FSH
- Issues of sponsorship and pharma partnership, creating CRFs and monitoring need to be addressed. Participants must have ultrasound capabilities and have WHO certificate for semen analysis

Secondly the idea of a pediatric-specific protocol was discussed at length but it was decided that this would be developed by Leo Dunkel and Mehul Dattani before brining to a larger discussion.

Monday June 30th

Consensus Statement for the Evaluation and treatment of CHH
Monday was a working day to develop the outline and principle points for the Consensus statement. Groups were divided into the following:
Clinical Presentation & Developmental view: Bouloux, Dwyer, Juul
Evaluation and Differential Diagnosis: Dattani & Quinton
Treatment & Management: Pitteloud & Young
The detailed outline and tables were drafted and will be submitted to editors to determine interest. Once we identify a target journal interested in the consensus statement the process will commence for validation and comment by the Clinical Working group.

Meeting Attendees:
Pierre Bouloux, Mehul Dattani, Leo Dunkel, Andrew Dwyer, Anders Juul, Nelly Pitteloud, Richard Quinton, Jacques Young