Health Economics Analysis Plan
(cost-effectiveness analysis plan)

SCIENCE – Stem Cell therapy in IschEmic Non-treatable Cardiac diseasE

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1. Introduction.

Ischemic heart disease (IHD) caused by coronary artery disease is currently the most common cause of death worldwide and a major cause of hospital admissions in industrialised countries. Classical therapies have contributed to a significant reduction in mortality, but there is an increasing number of patients with chronic IHD and/or heart failure without further treatment options. For these patients, stem cell therapy may be a viable therapeutic option through its capacity to regenerate their myocardial function. The stem cell product CSCC_ASC is a recent, promising treatment option which is currently not in routine use.
The aim of the SCIENCE project is to document the regenerative capacity of CSCC_ASC treatment in patients with chronic IHD or heart failure. A cost-effectiveness analysis will also be developed to estimate the cost of the intervention and relate this to the improvement in health resulting from the intervention. The cost-effectiveness analysis is the main focus of the present document.

2. Study design.

The SCIENCE clinical trial is a double-blind multi-centre placebo-controlled trial with two arms. Patients randomised to the intervention arm will receive an injection of CSCC_ASC into the heart based on a full mapping of the heart (Noga mapping procedure) performed immediately before the injection. Patients randomised to the control arm will receive placebo treatment consisting of injection with isotonic saline. There will be a 2:1 randomisation to intervention and control arm respectively of a total of 138 patients with 38 recruited in Denmark and 20 in each of the remaining five European centres. Patients with severe

ischemic heart failure are eligible to participate in the clinical trial (see the protocol for a full list of inclusion criteria).

The primary clinical outcome is left ventricle end-systolic volume at 6 months follow-up.

The cost-effectiveness analysis will be conducted alongside the clinical trial so that data on cost and effect in terms of level of health will be available for each individual patient enrolled in the trial [1,2]. The effect measure for the cost-effectiveness analysis will be quality-adjusted life years. Two complementary cost-effectiveness analyses will be performed: (1) a within-trial evaluation where cost and health effects of individual patients are limited to the one-year follow-up period in the trial and (2) a decision model approach where cost and health effects are modelled to enable the incorporation of longer term impacts of the intervention.

The primary outcome for the economic evaluation is the incremental cost-effectiveness ratio of CSCC_ASC treatment compared to placebo.

3. Study perspective.

The computation of cost-effectiveness ratios may be carried out from the point of view of society as a whole, or alternatively with other, more restrictive perspectives, such as the point of view of the healthcare sector. In the present study, both of these perspectives will be used.

4. Length of follow-up for clinical and economic endpoints.

Health events leading to resource utilisation in the hospital sector captured continuously from treatment until three years after from the case report form (CRF). Dead or alive is captured 1, 2 and 3 years after treatment, and health-related quality of life measurement on screening, at 26 weeks and 52 weeks after treatment using an EQ-5D questionnaire.

5. Data collection.

5.1. Costs.

<u>Capturing resource inputs.</u> The CRF will register for each patient enrolled clinical data and resource events at specific measurement points including the day of treatment with CSCC_ASC

(or placebo), one day before and after treatment followed by 4, 12, 26 and 52 weeks after treatment. Relevant resource events for each patient will be extracted from the CRF such as Noga mapping procedure, endocardial injection catheterization procedure, physical examination, drugs prescribed and procedures performed (electrocardiogram, ECHO scan, blood tests). The CRF may also be used to identify if patients have suffered a worsening of heart failure leading to hospitalisations including procedures performed and treatment given. These resource events will be valued as described below.

Unit cost of a CSCC-ASC treatment unit. The cell product CSCC_ASC will be given to all patients randomised to the intervention arm at all six participating study centres. Treatment units of CSCC_ASC will be produced in the The Cardiology Stem Cell Centre at Rigshospitalet University Hospital, Copenhagen, Denmark and subsequently transported to the participating study centres. The cost of producing a treatment unit of the cell product CSCC_ASC will be done using a micro-costing approach [3]. Staff at The Cardiology Stem Cell Centre will be interviewed to obtain information on the production process and the inputs required including materials, personnel time and laboratory equipment utilised. Data collected will be entered into Microsoft Excel and a spreadsheet will be developed to calculate the cost per treatment unit of CSCC_ASC. (This may later be used by partners outside Denmark to estimate the cost of producing treatment in their own countries.) Transportation cost of treatment units to partners outside Denmark will be estimated by obtaining the prices from the selected private courier.

Unit cost of intra-myocardial injection of CSCC_ASC. The treatment itself consists of an initial mapping of the heart using a catheter followed by injection of CSCC_ASC into relevant sections of the heart using a catheter with a needle. The cost of this procedure will be approximated by a relevant DRG tariff modified to capture the characteristics of the procedure including for instance specialised catheters and extra personnel time. Country-specific DRG tariffs will be identified for individual partner countries.

Unit cost of different hospital services in the follow-up period. Patients in both study arms may suffer spells of decreased health resulting in the need for seeking hospital care. The types

of spells of decreased health and hospital care provided will be captured from the CRFs during the follow-up period. Individual unit cost for a specific hospital intervention/procedure will be approximated by the DRG tariff used for that specific intervention/procedure. Possible interventions include insertion of pacemaker or management of ventricular tachycardia. Country-specific DRG tariffs will be identified for individual partner countries.

5.2. Effects.

Effects will be captured at the individual patient level as part of the multi-centre controlled trial. Quality-adjusted life years measured as their EQ-5D value obtained at the time of screening, at 26 weeks and 52 weeks after treatment using an EQ-5D questionnaire. The measurement of quality-adjusted life years at 52 weeks will be used for the cost-effectiveness analysis.

6. Analysis.

6.1. Cost-effectiveness analysis alongside clinical trial (within-trial evaluation).

At the end of the clinical trial, cost and effects are available for each participating patient [1]. Cost of an individual patient for the period from treatment until the end of the one-year follow-up will be estimated as follows for the intervention group:

$$C_i = c^p + c^t + \sum_a S_i^a * c^a$$

where C_i is the total cost of patient *i* in the intervention group until the end of the follow-up period, c^p is the unit cost of one treatment of CSCC_ASC, c^t is the unit cost of the combined mapping of the heart (Noga mapping procedure) and subsequent injection of CSCC_ASC (endocardial injection catheterization procedure), S_i^a is a dichotomous variable taking the value 1 if patient *i* has experienced a spell of decreased health (complication) of type *a* in the follow-up period and 0 otherwise and c^a is the unit cost of treating or managing illness spell (complication) of type *a*. Similarly, cost of an individual patient from the control group is:

$$C_j = \sum_a S_j^a * c^a$$

with a similar interpretation as above. The effect on individual patients will be their quality-adjusted life years measured as their EQ-5D value obtained at the end of the one-year follow-up denoted E_i for patient *i* in the intervention group and E_j for patient *j* in the control group. The point estimate of the incremental cost-effectiveness ratio (ICER) will be calculated as:

$$ICER = \frac{\overline{C_i} - \overline{C_j}}{\overline{E_i} - \overline{E_j}} = \frac{\Delta C}{\Delta E}$$

where $\overline{C_i}$ and $\overline{C_j}$ are the arithmetic mean costs among patients in the intervention arm and control arm respectively. Similarly, $\overline{E_i}$ and $\overline{E_j}$ are the arithmetic mean quality-adjusted life years in the intervention arm and control arm.

The ICER may be assessed against an accepted cost-effectiveness threshold (national and international).

6.2. Uncertainty of the ICER.

6.2.1. Data uncertainty. The uncertainty of the ICER point estimate will be quantified using appropriate methods which will depend on the distributional characteristics of cost and effects.

If incremental costs and effects are distributed bivariate normal, a confidence interval for the ICER based on Fieller's method [4,5] may be calculated using the formula:

$$CI_{(1-\alpha)\%} = \frac{(\Delta C \Delta E - t^2_{\alpha/2}\rho se_c se_e) \pm [(\Delta C \Delta E - t^2_{\alpha/2}\rho se_c se_e)^2 - (\Delta E^2 - t^2_{\alpha/2} se_e^2)(\Delta C^2 - t^2_{\alpha/2} se_c^2)]^{0.5}}{\Delta E^2 - t^2_{\alpha/2} se_e^2}$$

where α is the significance level, $t^2_{\alpha/2}$ is the $(\alpha/2)$-fractile in a t-distribution, ρ is the correlation coefficient between ΔC and ΔE, and finally se_c and se_e are the standard errors of ΔC and ΔE respectively.

6.2.2. Bootstrapping methods. In accordance with current practice, the uncertainty associated with data may be further investigated by computing ICER for a large number of subsamples, thereby obtaining an empirical distribution of cost-effectiveness ratios, which not only gives an alternative estimate of the confidence interval but also makes it possible to study the distribution in a more detailed way [6,7].

6.2.3. Cost-effectiveness acceptability curves represent still another way of displaying the inherent uncertainty connected with data collection and subsequent computation. The curves display the estimated probability of regarding the intervention as cost-effective at any given threshold level for the ICER [8,9].

6.2.4. Expected value of perfect information. Further information about the impact of uncertainty can be obtained from the computation of the difference between the gains (depending on the choice of perspective) to be obtained if perfect information was available and the expected gains obtained after data collection [10,11].

6.2.5. Sensitivity analysis. While the above methods are designed to exhibit the data uncertainty in the analysis, uncertainty coming from choice of method, use of externally given parameters etc. will not be displayed and must be analyzed separately. This is done by carrying out alternative computations with different values of crucial parameters and/or slightly changed formulation of the basic computational model. Both univariate and multivariate (probabilistic) sensitivity analyses will be conducted [12].

6.3. Decision model analysis.

In order to assess the economic impact of the intervention, it is necessary to analyze cost, effects and to compute ICER over time intervals stretching beyond trial period [10]. To study the long-term perspectives and to find ICERs in this context, a Markov model will be used, with each cycle consisting of death and relevant events (unchanged myocardial function, worsening of heart failure and myocardial infarction). The necessary data for the Markov

model, in particular the transition probabilities, will be determined partly from the data of the clinical trial, partly from the literature.

6. 4. Cross-country analyses of ICERs involving partner countries. The computation of ICERs will be performed for each of the participating partner countries separately, but following up on this, a comparison will be made of the results obtained in each country, tracking the possible differences to differences in cost and methods of treatment of subsequent cases of heart disease. It systematic differences appear, they will be the object of specific analyses.

7. References.

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Production Cost of Stem Cell Treatment Units

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Background

The SCIENCE project has as its overall aim the implementation of an effective stem cell-based therapy to improve myocardial function in patients with ischemic heart disease and heart failure. As a part of the project for clinical therapy with allogeneic adipose-derived stromal cells (ASCs), a manufacture facility for centralized production of allogeneic ASCs has been set up.

The following is a note on the production cost of ASC. Knowledge of the cost of producing a treatment unit of ASCs is important since it enters as a basic ingredient for the cost-effectiveness analysis of stem cell treatment.

Determining unit costs poses some both theoretical and practical problems. These problems are connected with the nature of production processes, where some activities can be directly attributed to the units produced, whereas other activities are shared with other products or with production in other intervals of time. All ways of separating such shared activities and their cost into different parts related to each activity involves some element of arbitrariness, and the results obtained should be seen in this light.

The production process

A necessary first step in the determination of unit cost is to identify the basic steps in producing a treatment unit of ASC. Stem cells are initially extracted from donors, after which they undergo several procedures, in the course of which the original material is considerably expanded. The steps in the production of final treatment units are the following:

1. *Donor investigation.*
2. *Extraction of stem cells from donor.*
3. *Cleaning of extracted stem cells.*
4. *Bioreactor expansion phase 1*
5. *Bioreactor expansion phase 2*
6. *Control and validation of received material.*

In the following we consider the costs incurred in each of these 6 steps. Technically, we consider a batch of 320 treatment units of ASC. This number corresponds to current capacity with 2 bioreactors each running 360 days, and corresponds to 8 production cycles running through the steps 1-6.

The cost components

Taking the above distinction between 6 steps of production, we here outline the cost components, restricting attention to the most important items. For all details of the cost calculation the reader is referred to the spreadsheet costOfStemCells.xlsx.

1. Stem cells are obtained from donors, and before a donor is selected, some initial health checks are needed (blood test etc.). For the initial examination of 8 donors, there is a cost of DKK 52,084, of which 28,000 is cost of staff and 24,000 is use of materials, to which is added a minor amount for capital charges.

2. Extraction of stem cells from donors is done as a lard suction, which is a standard procedure of a plastic surgeon, and it is accounted for by its price, which is DKK 15,900 per case, giving a total of DKK 127,200. To this is added the cost of transporting the material from the surgeon to the laboratory, giving a total of DKK 138,400.

3. Cleaning of extracted stem cells is performed in a specialized room. The labour input in the cleaning process, assessed at current wage rates, gives a cost of DKK 68,000, to which comes materials to the amount of DKK 32,022. The equipment used gives rise to a capital cost of DKK 10,502, so that total cost at this step is DKK 110,524.

4. In the first round of expansion, the use of staff gives a cost of DKK 212,000, whereas the use of materials is considerable and costs DKK 588,142. Here again, a costly equipment is in use, and the cost to the batch is DKK 122,902, giving a total of DKK 923,044.

5. The second round of bioreactor expansion is more demanding than the first one, involving in-process control and freezing down of the cells. Here we incur a cost of DKK 1,920,000 for staff, 3,005,754 for materials and 430,157 for equipment use, in total DKK 5,355,911.

6. The final validation gives rise to a cost of DKK 49,237.

Total cost and unit cost

Summing total cost of the six steps, we obtain a total cost of DKK 6,629,199 for a batch of 320 units. This corresponds to a cost of DKK 20,716 per treatment unit.

Concluding comments

The general reservations against unit cost calculations have been mentioned, at this point it should be noticed that some of the items in the calculation, such as those connected with use of capital equipment, are based on assessments which are in their nature imprecise.

It should of course also be added that all the cost valuations are based on Danish wages and prices, a natural choice given that production is placed in Denmark.