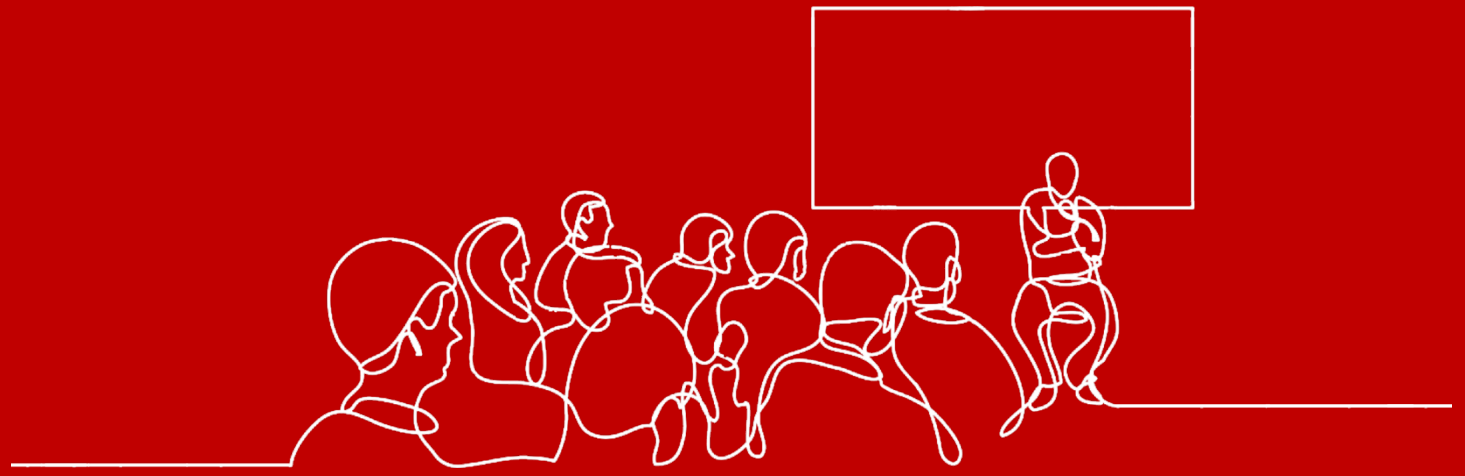


Empowering Research Seminar Series

Danielle Daft and Emma Cutting

Barker lab

From concept to clinical trial

wellcome-MRC cambridge stem cell institute

STEM-PD

From Concept to Clinic

Intrastriatal transplantation of human embryonic stem cell (hESC) derived dopaminergic cells for Parkinson's disease

Danielle Daft
Research Manager

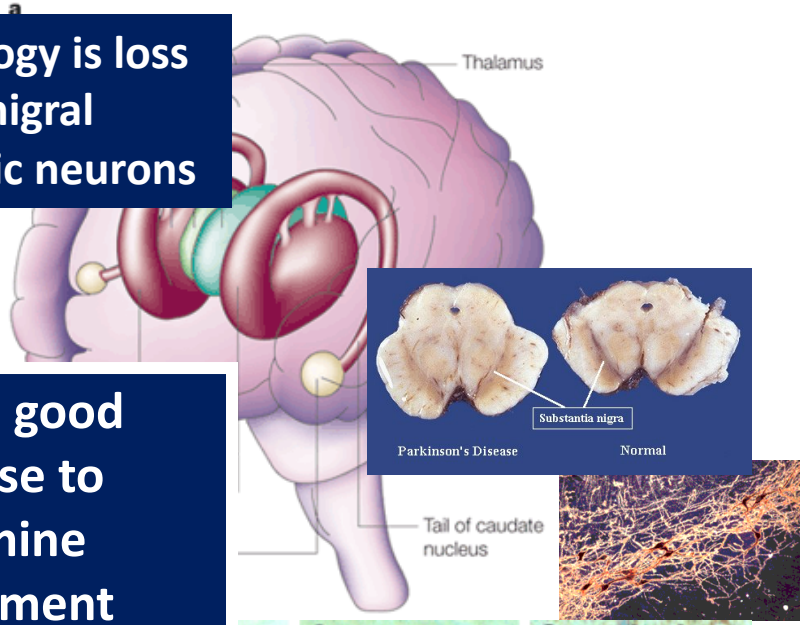
Emma Cutting
Senior Clinical Trials Coordinator

30th April 2020

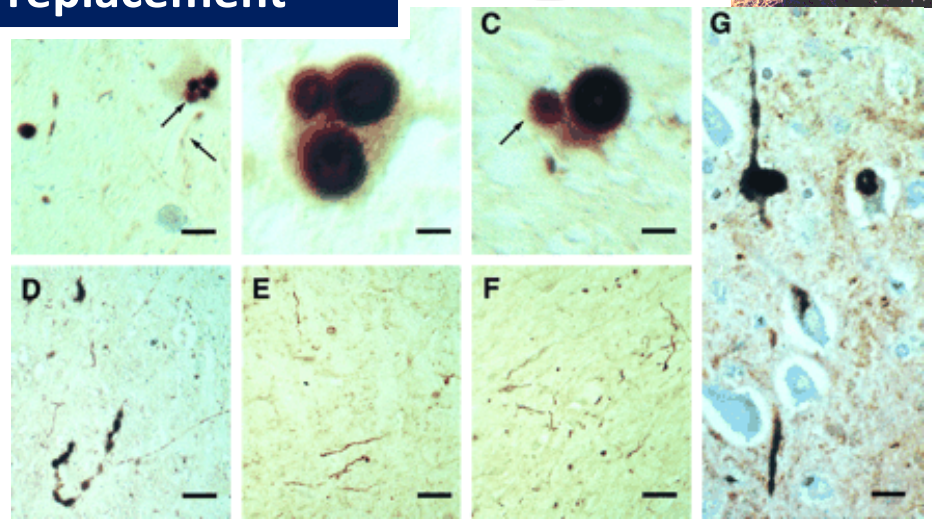
wellcome-MRC cambridge stem cell institute

Rationale for choosing and treating Parkinson's disease with cell based therapies

Core pathology is loss of the nigral dopaminergic neurons



... and a good response to dopamine replacement



... so a dopamine cell therapy will help these aspects of disease, and:

(a) Replace dopamine where it is needed so avoid the off target effects of drugs

(b) Release dopamine in physiological way and so avoid long term complications of L-dopa therapy

... BUT NOT A CURE!

wellcome-MRC cambridge stem cell institute

History of trials

The New England Journal of Medicine

TRANSPLANTATION OF EMBRYONIC DOPAMINE NEURONS FOR SEVERE

Review > Lancet Neurol. 2013 Jan;12(1):84-91. doi: 10.1016/S1474-4422(12)70295-8.

Fetal Dopaminergic Transplantation Trials and the Future of Neural Grafting in Parkinson's Disease

Roger A Barker [1], Jessica Barrett, Sarah L Mason, Anders Björklund

Affiliations + expand

PMID: 23237903 DOI: 10.1016/S1474-4422(12)70295-8

A Double-blind Controlled Trial of Bilateral Fetal Nigral Transplantation in Parkinson's Disease

C. Warren Olanow, MD,[1] Christopher G. Goetz, MD,[2] Jeffrey H. Kordower, PhD,[2] A. Jon Stoessl, MD,[3] Vesna Sossi, PhD,[3] Mitchell F. Brin, MD,[1] Kathleen M. Shannon, MD,[2] G. Michael Nauert, MD,[4] Daniel P. Perl, MD,[5] James Godbold, PhD,[6] and Thomas B. Freeman, MD[4]

RESULT
No significant benefit at 2 year using UPDRS defined OFF
GIDs seen in 54% of patients

SO WHY IS THIS?
INTERROGATED THE
- IDENTIFIED CRITICAL FACTORS ....

ient selection
sue prep and
plantation
pe and duration of immunosuppression
4. **Length of follow up**

... AND DESIGNED NEW TRIAL ...

wellcome-MRC cambridge stem cell institute

TransEUro

2010

OPTIMISED PATIENT SELECTION
- Patients <65 years old
- <10 years duration
- Minimal LIDs
- Form an observational cohort
- N=150

STANDARDISED TISSUE PREPARATION

OPTIMAL GRAFTING PROCEDURE:
- Delivery of tissue using 5-7 tracts to post putamen
- Rehncrona instrument for grafting

2015 - 2018

- 11 grafted (05/15 to 03/18) and immunosuppression for 12 months post second graft
- 20 followed with PET
- 110 followed clinically
- Motor assessments rated blindly

3 year primary end point (UPDRS OFF)

Many secondary end points

Blinded video ratings

2021

But, where next given ethical and logistical problems with fetal tissue?

87 surgical slots lost because of tissue supply

TRANSEURO

wellcome-MRC cambridge stem cell institute

Key points to consider when developing a new stem cell therapy

- Cell type to use – consent process, where the cells have been derived
- Intellectual property – who owns the key IP for the cell product, the protocol for processing cell – needs locking down. Important to have access to this
- Funding – where is the funding for the preclinical and clinical work coming from? Not cheap!
- Delivery device – how will you deliver your therapy?
- Preclinical studies – show improvement over standard of care
- Cell production – GMP standard
- Clinical Trial design – Phase 1

wellcome-MRC cambridge stem cell institute

STEM-PD

Intrastriatal transplantation of Human embryonic stem cell (hESC) derived dopaminergic cells for Parkinson's disease (PD)

Cell product

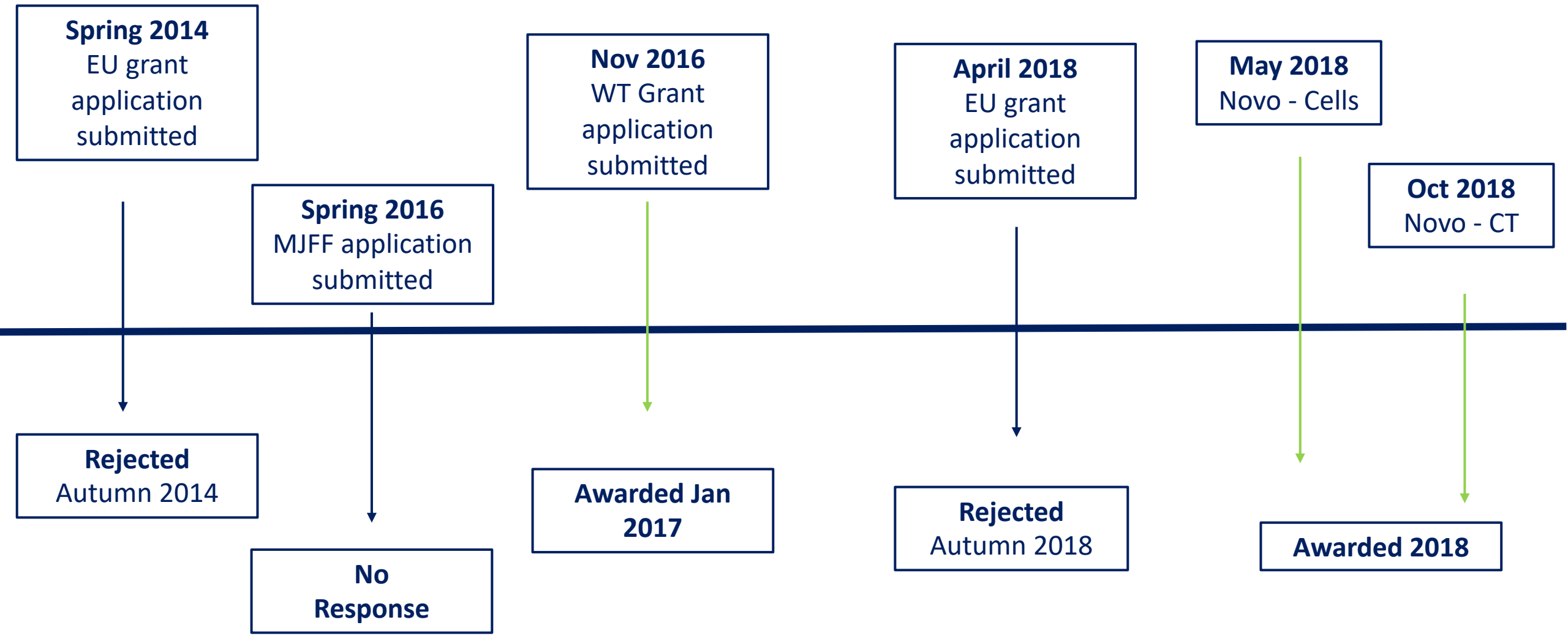
- Human embryonic stem cell-derived midbrain dopaminergic progenitor cells (cryopreserved)
- Clinical-grade stem cell line **RC17**
- The cell product is manufactured through directed differentiation of pluripotent RC17 hESCs for 16 days using a ventral midbrain differentiation protocol
- After differentiation, the cells are cryopreserved in vials with 5 mill cells per vial
- This product is classified as an **ATMP.**
- **Route of administration**: Transplantation to the putamen by stereotaxic implantation (bilateral)

Device

- Based on the previous device which was used within the Transeuro study
- Undergoing: prototype manufacture, verification, validation, full technical file documentation and regulatory work
  – partnering with CDP
- Novo Nordisk is facilitating the development of TRN6 from a design to a medical device suitable for use in clinical trials across the globe

wellcome-MRC cambridge stem cell institute

STEM-PD: application process



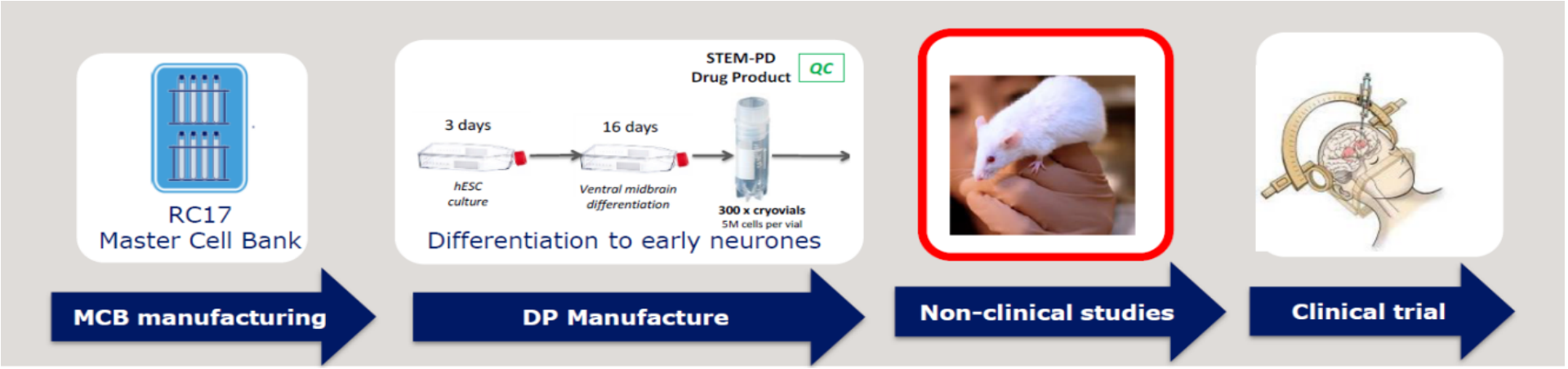
wellcome-MRC cambridge stem cell institute

STEM-PD: cells

Preclinical studies are on-going / being initiated

Current Status:

- GLP safety/toxicology testing being completed by Envigo (Huntingdon).
- This batch of cells will also be in the clinical trial



Spring 2019

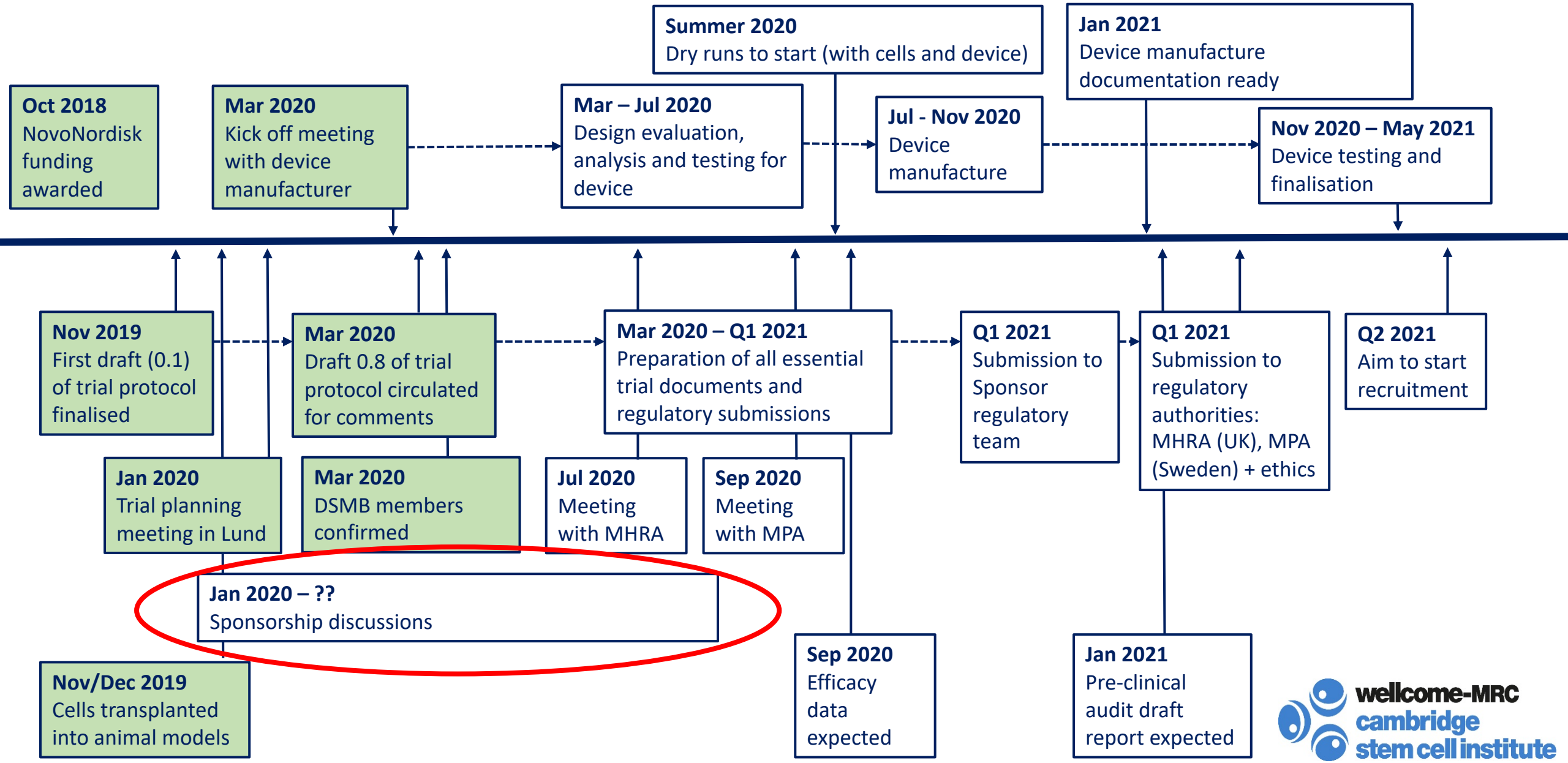
Batch #1: Aug 2019
Batch #3: Oct 2019

Batch #3: Nov 2019

FHD Q2 2021 (Batch #3)

wellcome-MRC cambridge stem cell institute

STEM-PD: timelines



wellcome-MRC cambridge stem cell institute

STEM-PD: trial sponsorship

Sponsor

- The individual, or organisation (or group of individuals or organisations) that takes on responsibility for confirming that there are proper arrangements in place to initiate, manage and monitor, and finance a study. Responsibilities are defined by the Research Governance Frameworks and by the Clinical Trials Regulations.
- **This is different from the funder!**
- In Cambridge, usually CUH (+/- UCAM)

Initial plan

- Two single-site, parallel studies (UK and Sweden)
- Independent sponsorship
- 8 participants across the two studies
- Data (including safety) shared between the two
- **But**, the MHRA was not favourable to this

New proposal

- Co-sponsored trial, where Cambridge and Lund will be sponsors on a single trial – 4 in total
- Will need clear division of responsibilities etc.
- Provisionally agreed, but will need a lot of negotiation!

wellcome-MRC cambridge stem cell institute

STEM-PD: trial sponsorship

At minimum, the agreement will need to cover:

Authorisation for the clinical trial and research ethics committee opinion

- Obtain required authorisations to commence the trial (clinical trial authorisation and favourable ethics committee opinion)
- Keep records of all amendments to the authorisations and obtain approval where approvals are required
- Produce undertaking to allow inspection of premises
- Notify all relevant bodies of the conclusion or termination of the trial within the specified timeframes

GCP and the conduct of clinical trials

- Ensure that the conditions and principles of Good Clinical Practice are satisfied and adhered to
- Ensure that the trial is conducted in accordance with the protocol and subsequent amendments
- Notify any serious breaches of Good Clinical Practice or the protocol, or any urgent safety measures taken to the appropriate authorities
- Ensure investigational medicinal products and relevant devices are available to subjects free of charge
- Keep a trial master file to hold all documents relating to that trial
- Appoint named individuals responsible for archiving the trial essential documents

Pharmacovigilance (safety reporting)

- Ensure an investigator's brochure exists and is validated and updated at least annually
- Keep records of all adverse events relating to that trial which are reported by investigators
- Record and report suspected unexpected serious adverse reactions to appropriate authorities within specified timelines
- Ensure all suspected unexpected serious adverse reactions are entered into the European database
- Provide annual list of suspected serious adverse reactions and a safety report to the appropriate authorities

Manufacture and labelling of investigational medicinal product and investigational device

- Meet requirements for the authorisation to manufacture and import investigational medicinal product
- Certification of the investigational medicinal product by a Qualified Person
- Two-step release process for investigational medicinal product ('technical release' and 'regulatory release')
- Ensure investigational medicinal product is labelled in accordance with Article 15 of Commission Directive 2003/94/EC

wellcome-MRC cambridge stem cell institute

STEM-PD: the team

Project lead: Malin Parmar
Project management: Emma Cutting, Danielle Daft, Trinette Van Vliet
Pre-clinical: Agnete Kirkeby, Jenny Nelander Wahlestedt, Deirdre Hoban, Xiaoling He, Shaline Fazal, Venkat Pisupati
Surgery: Hjálmar Bjartmarz, Rob Morris, Mike Hart
Clinical: Roger Barker, Håkan Widner, Gesine Paul-Visse
Regulatory: Boyd Consultants (Kim Champion, Julie Warner, Ben Jacoby)
Clinical trials unit support: Louise Stockley, Carrie Bayliss, Ulf Malmqvist, Ingegerd Dalfelt
R&D/governance: Stephen Kelleher, Carolyn Read
Contracts: Tracey Hensman, Mona Alexander
IP: Dafne Chirivino
Imaging: Paola Piccini, Ruben Smith, Oskar Hansson
Device: Clinical Engineering Innovation (Rachael Andrews, Sarah Greasley, Paul White, Danny Marsden), Cambridge Design Partnership
Advisory: Anders Björklund, Olle Lindvall
Administrative: Paulina Pettersson
Statistics: Stan Lazic
Funding: Novo Nordisk

wellcome-MRC cambridge stem cell institute